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Neuro-Oncology Practice Clinical Debate: targeted therapy vs conventional chemotherapy in pediatric low-grade glioma

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Abstract

The treatment of children with low-grade glioma has evolved over the last several decades, beginning initially with focal radiotherapy, which has now been largely replaced by systemic treatment with conventional chemotherapy agents or more recently molecularly targeted therapeutics. A consensus standard of care is not well defined, leaving clinicians and parents to choose from an increasing number of options, often without complete information concerning the associated risks and benefits. Issues critical to this topic include timing of interventions (when to treat), preservation of neurological function (goals of treatment), choice of initial therapy strategy (conventional cytotoxic chemotherapy vs molecularly targeted therapy), duration of treatment (how long, and what clinical or imaging endpoints to consider), and perhaps most important, risk reduction relative to anticipated benefit. The groups from the University of California, San Francisco and Dana Farber Cancer Institute, moderated by Michael Prados, herein debate the merits of cytotoxic chemotherapy and targeted therapeutics as initial treatment strategies in pediatric low-grade glioma, a topic discussed daily in Tumor Boards across the United States and abroad. Prospective, randomized, phase 3 trials comparing the 2 strategies, conducted within homogenous disease settings, with consistently evaluated functional and imaging endpoints, are not available to guide the risks/benefit discussion. As is often the case in rare biologically diverse diseases, in a vulnerable population, therapy decisions are frequently based on incomplete data, physician experience, bias to some degree, and patient/family preference.

Keywords:

chemotherapy | glioma | neuro-oncology | pediatric | pilocytic astrocytoma.

Clinical Scenario

A previously healthy 10-year-old girl presents with new-onset headaches and visual symptoms. On eye examination, she had decreased visual acuity and a visual field defect in one eye. Imaging reveals a large, cystic, enhancing complex mass in the chiasmatic/hypothalamic region consistent with an optic pathway glioma (OPG) with associated mild hydrocephalus. Cyst decompression with a biopsy revealed a pilocytic astrocytoma, WHO grade I, with a BRAF activating

fusion (*KIAA1549-BRAF*). There was no stigmata or history of neurofibromatosis type 1. Over several months of careful observation and close imaging follow-up, the solid component of the tumor increased in size with associated decrease in visual acuity from baseline. Treatment was recommended because of the clinical and radiographic progression. Would you initially recommend a regimen of conventional cytotoxic chemotherapy or a targeted, Ras pathway inhibitor?

WHO grade I and II gliomas are the most common CNS tumor in children.[1] Survival outcomes are generally excellent, with 20-year overall survival rates reported between 87% and 91%.[2,3] OPGs are generally considered a common subtype of pediatric "low-grade" gliomas (pLGGs); they represent approximately 5% of pediatric brain tumors and the majority are pilocytic astrocytomas.[4,5]

Similar to the promising survival curves of other LGGs, 20-year overall survival for childhood OPG (>3 years) has been described to be as high as 98%.[2] Unfortunately, the majority of children suffer long-term visual impairment.[6,7] In adult survivors of LGG including OPGs, bilateral blindness is associated with reduced chances of living independently, getting married, and finding employment.[8] Furthermore, OPGs that affect hypothalamic structures are associated with increased risk of neuroendocrine deficits.[9] As a result, therapy for pediatric OPGs should aim to reduce tumor-associated morbidity while preserving excellent survival and minimizing potential toxicities.

Pro–Targeted Therapy View (Drs Cooney, Kline, and Mueller)

To date, chemotherapy regimens have remained the predominant treatment modality for OPGs. The combination of carboplatin and vincristine (CV) is widely considered standard, first-line treatment for pLGGs, inclusive of OPGs,[10] and carries a 5-year progression-free survival (PFS) of 46%.[11] Alternative chemotherapy regimens have been developed in recent decades, but without robust improvements in PFS. Additionally, PFS has historically focused only on radiographic measurements and fails to address the potential lack of correlation between imaging and visual deficits.[12] In previous clinical trials using standard chemotherapy, neuro-ophthalmic outcomes have been scarcely reported (if at all), making it impossible to know whether chemotherapy is effective at preserving vision. In fact, one systematic review describing the effect of chemotherapy on visual outcomes in 174 children found vision improvement in less than 15% of patients, leading authors to conclude that chemotherapy did *not* improve visual outcome in these children.[13]

In contrast to the unknown impact on vision, the side effects of standard chemotherapy are well known. Rates of hypersensitivity reactions to carboplatin have been reported as high as 40%,[14] whereas a recent study cited neurologic toxicity in 86% of pediatric patients treated with CV—twice as high as prior reports.[15] Further, patients undergoing treatment with standard chemotherapy are at risk for blood count suppression, infection, and complications related to central lines.[16] Therefore, choosing conventional cytotoxic chemotherapy for the current patient comes with a high likelihood of associated toxicity without a known benefit to her vision.

At least 70% of pilocytic astrocytomas possess a tandem duplication at 7q34 resulting in a fusion gene of *BRAF* (encoding the B-Raf proto-oncogene) with *KIAA1549*. The subsequent fusion protein includes the N′-terminal of KIAA1549 and the truncated C′-terminal of BRAF, leading to constitutive activation of the BRAF kinase with downstream activation of MAPK signaling.[17,18] *KIAA1549-BRAF* rearrangements have established themselves as the most frequent somatic driver alteration in pediatric pilocytic astrocytomas[19] and provide a point of vulnerability to MAPK pathway inhibition.

Treatment of pLGGs with targeted therapy is a strategy that began in the last decade, and continues to develop. One of the first targeted agents used in a phase 2 pediatric trial was sorafenib, a multikinase BRAF, VEGF receptor, platelet-derived growth factor receptor, and c-kit inhibitor. Sorafenib unfortunately led to rapid disease progression in children with BRAF fusion tumors, later explained by the paradoxical activation of MAPK signaling.[20,21] Thus, we learned to avoid first-generation BRAF inhibitors in BRAF fusion–positive tumors. Second-generation BRAF inhibitors, which target both monomeric and dimeric forms of the BRAF oncoprotein and circumvent paradoxical activation, have since come in to development.[22] A pediatric phase 1/2 of an oral pan-RAF kinase inhibitor that targets both monomeric and dimeric forms of the BRAF oncoprotein, TAK580 (formerly MLN2480), is currently being run by the Pacific Pediatric Neuro-Oncology Consortium and is enrolling children who have progressed after chemotherapy or radiation (NCT 03429803).

MEK inhibitors are proving to be another effective strategy against BRAF fusion pLGG. Selumetinib (AZD6244), a selective orally available, non-ATP competitive small-molecule inhibitor of MEK-1/2, has now been widely studied. The Pediatric Brain Tumor Consortium has published results of a phase 1 trial of selumetinib in pediatric patients with recurrent or refractory LGG, demonstrating a 2-year PFS at the recommended phase 2 dose (RP2D) of 69% ± 9.8%. Among the 5 of 25 patients with sustained partial response at the RP2D, 4 had BRAF aberrations (2 *KIAA1549-BRAF* fusion) and 1 had insufficient tissue.[23] The results led to an ongoing Pediatric Brain Tumor Consortium phase 2 trial (NCT01089101). Interim results on 1 of 3 strata that have already completed enrollment showed children with non-neurofibromatosis type 1 optic pathway/hypothalamic WHO grade I or II glioma demonstrated a 2-year PFS of 65 ± 13%.[24]

Similar to selumetinib, trametinib is an oral, commercially available, highly selective allosteric inhibitor of MEK-1/2, approved by the FDA in 2013 for single-agent use in adult patients with unresectable or metastatic, *BRAF*^{V600E}, or ^{V600K}-mutated melanoma. A pediatric phase 1 trial of trametinib in patients with recurrent or refractory solid tumors proved safe and tolerable, with an RP2D of 0.025 mg/kg daily for patients age 6 years or older. Median treatment duration was 81 weeks for the 40 patients enrolled on single-agent therapy, 53% of whom remained on treatment at time of publication.[25] A trial using trametinib in pediatric patients with *BRAF*-fusion

low-grade astrocytomas showed a minimum of stable disease in 70% of patients, all of whom had durable responses lasting more than 1 year (NCT02124772).[26]

Of most relevance to our patient, trametinib led to decreased tumor size and improved or stable vision in several reports of children with hypothalamic optic pathway pilocytic astrocytoma with *BRAF* fusion.[27–29] Although recognizing that neuro-ophthalmologic outcome data for the use of MEK inhibition against pediatric OPG has yet to be available from the aforementioned clinical trials, we argue the potential benefit of trametinib is convincing when compared with the proven lack of benefit from conventional chemotherapy.

Although overall well tolerated, we give serious consideration to the toxicity profiles of MEK inhibitors that include rash, cardiac dysfunction, skin infections, creatine phosphokinase elevation, and ocular toxicity.[23,24,26] Of particular importance in children with OPGs is ocular toxicity. MEK inhibitor-related retinopathy is a rare complication best characterized in adult melanoma patients.[30] Selumetinib-related outer retinal layer separation has been reported in only 2 children, and resolved without visual sequelae.[31] Meanwhile, there have been no published reports of trametinib-related ocular toxicity in children. Because ophthalmologic evaluations are critical components of OPG surveillance, their frequency allows for early detection of any ocular toxicity related to MEK inhibition.

Our understanding of tumor biology along with development of targeted agents has expanded our therapeutic options for pediatric brain tumors with MAPK pathway aberrations. The proof of superior efficacy and tolerability of molecularly targeted therapy over conventional chemotherapy for optic pathway pilocytic astrocytomas will come only from results of randomized trials with rigorously defined tumor biology and functional endpoints. An example of such a trial is the upcoming SIOP (International Society of Paediatric Oncology)-Low Grade Glioma In Children (LOGGIC) study, which will compare standard chemotherapy with a targeted agent, with visual function as a primary study endpoint. Fortunately the safety, tolerability, and guidelines for dosing of trametinib for children and adolescents have now been well described. Furthermore, targeted therapy reduces inpatient stays, clinic visitations, and intravenous access as compared with standard chemotherapy.[28] Such impacts on quality of life should be weighed heavily when considering the long-term disease control these patients often require. In conclusion, we recommend use of the targeted MEK inhibitor for the treatment of this 10-year-old girl with a progressive optic pathway pilocytic astrocytoma positive for *KIAA1549-BRAF* fusion.

Pro–Chemotherapy View (Drs Yeo, Haas-Kogan, and Chi)

Whereas advancement in molecular genomics has substantially improved our understanding of tumor biology and allowed for identification of unique molecular therapeutic targets, development of targeted therapies for the majority of patients with pLGG are plagued by several challenges. These include a lack of suitable drugs for many genetic alterations, innumerable pathways of resistance, unique toxicities of currently available biologics, and the unknown long-term effect on growth and development.[32,33] Conversely, conventional chemotherapy has been used safely and effectively in the treatment of pLGG over the past 2 decades, surpassing radiation therapy as the treatment of choice.[34–37] We believe that chemotherapy, based on the reasons stated below, should remain the upfront treatment of choice for patients with pLGGs.

There is a large body of evidence supporting the use of chemotherapy, with a myriad of chemotherapeutic regimens for pLGG described in the literature. These regimens include CV; thioguanine/procarbazine/lomustine/vincristine; monotherapy vinblastine; bevacizumab; and monthly carboplatin; among others.[16,38–40] Although they vary in side effect profiles and response rates, the vast majority of these regimens are generally well tolerated, efficacious, and have excellent long-term outcomes.[37,41] These results are substantiated by Bandopadhayay et al, who described the long-term outcomes of more than 4000 children with pLGG treated during the chemotherapy era; the 20-year irradiation-free overall survival for this cohort was greater than 90%.[3] In contrast, the outcomes of targeted therapy in pLGG are relatively unknown. Although there are abstracts and anecdotal reports of good response on various early-phase clinical trials and off-label use, there remains a paucity of evidence in the literature to date describing the efficacy and safety of these agents.[28]

The duration of therapy is well established for most chemotherapeutic regimens but remains unknown for regimens involving targeted agents. Most patients receive 1 to 2 years of chemotherapy with resultant disease stabilization prior to therapy cessation and are typically managed observantly thereafter. Conversely, the majority of targeted therapies for pLGG are still being tested in early-phase clinical trials and the optimal duration of therapy is thus unclear. As a result, many practitioners have adopted the strategy of continuing targeted therapy indefinitely, provided that treatment is tolerated without significant adverse effects and with continued response/disease stabilization. In cases in which targeted therapy for pLGG has been discontinued, there are indications that the majority of patients suffer disease progression/recurrences shortly following cessation of therapy. This is consistent with the experience with BRAF and MEK inhibitors seen in adults with melanoma, and as such, present practitioners with a therapeutic dilemma, given the relatively unknown long-term effects of these drugs.[42]

The considerable experience treating pLGG using chemotherapeutic agents over the past several decades has demonstrated the relative safety of these conventional regimens. Although many of these agents are associated with various common chemotherapy-related side effects, with the exception of alkylator agents, the risk for significant long-term sequelae from these agents is relatively low. On the contrary, the long-term effects of targeted therapies remain to be elucidated.[43] In addition,

even in the short term, targeted therapies are associated with significant off-target adverse effects. MEK inhibitors and BRAF inhibitors (both commonly used in pLGG), for example, are associated with significant cardiomyopathy of unclear etiology, cutaneous skin reactions, and ocular toxicities.[44] This was recently highlighted in the phase 1 study of selumetinib in pediatric patients with LGGs, in which a high proportion of patients (17 out of 38) discontinued treatment because of toxicity or patient/physician preference.[23] More important, the effects of these drugs on the growth and neurodevelopment of young children are unknown.

In addition to the safety and efficacy of chemotherapy in the treatment of pLGG, the relatively nondiscriminatory mechanism of action of chemotherapy is advantageous, as it allows for treatment across histology and molecular subgroups. Whereas targeted therapies are limited by multiple mechanisms of resistance and the intricacies of cellular pathways, there are no known resistance patterns specific to chemotherapy in pLGG. There is evidence in clinical practice that the failure of a particular regimen such as carboplatin/vincristine does not affect the potential efficacy of monotherapy vinblastine[42] and vice versa. Additionally, patients who develop progression or recurrence of disease after completion of a previously efficacious regimen will typically have similarly good response to the same regimen following reinitiation of chemotherapy.

Targeted therapy represents the dawn of a new era and the realization of the promise of personalized medicine, in which precision in therapeutic targeting hypothetically leads to significantly fewer side effects. However, the inherent specificity of this therapy type forms the basis of several clinical challenges. Although BRAF inhibitors have proven to be exceedingly active against gliomas with *BRAF*^{V600E} mutations, this mutation represents only approximately 10% of pLGGs.[32,37] For most of the other non-BRAF–activated pLGGs (eg, *MYB*, FGFR), the ideal therapies are either untested or have not yet been developed. Moreover, for the most common genetic alteration in pLGG, BRAF:KIAA1549 fusion, the failure of a recent phase 2 clinical trial of sorafenib because of secondary paradoxical activation is a sobering reminder of the complexity of cellular pathways.[21,43] More recently, the development of a new phase 1 clinical trial of a second-generation BRAF inhibitor offers renewed optimism for patients with such fusion. Preliminary results from this trial are pending.

In summary, whereas targeted therapy holds immense potential for improved clinical response and curative regimens with minimal secondary effects, the development of these drugs is still in its infancy. Therefore, although the importance of these developments cannot be understated, the role of targeted therapy in the upfront treatment of pLGG is unclear. With the outstanding long-term outcome, excellent safety profile, minimal long-term side effects, and experience with the use of chemotherapy, together with the many unknowns associated with targeted therapy at this point, we believe conventional chemotherapy should remain the upfront treatment of choice for pLGG.

Pro–Targeted Therapy Reply (Drs Cooney, Kline, and Mueller)

We appreciate the thoughtful stance taken by the team at Dana Farber Cancer Institute, and understand conventional chemotherapy has a long-standing history as front-line use for the treatment of pediatric OPG. However, we believe the knowledge of molecular drivers and development of targeted therapies that has arisen in the last decade should be capitalized on now, to improve on standard of care.

The question of how long a patient with an OPG should be treated is yet unanswered, regardless of therapeutic choice. Clinical response has been reported as soon as 17 weeks on trametinib therapy,[28] and most reports document trametinib treatment duration of at least 18 months. This is in comparison with conventional chemotherapy regimens, which most frequently span 1 year and carry unclear benefit in decreasing tumor-related morbidity. The optimal duration of therapy for targeted agents that would yield sustained, functional response while minimizing resistance and treatment-related toxicities remains unknown. In the presence of neuro-ophthalmologic stability, we would treat with trametinib for a minimum 12 months' duration—arguably a similar treatment length as standard chemotherapy. Should our patient tolerate her initial course and suffer recurrence posttreatment cessation, we would resume therapy with trametinib.

We also acknowledge late effects of targeted agents are not fully understood, and may not be for decades. Still, there are substantial toxicity data from a breadth of phase 1/2 clinical trials in adults and children alike to fully understand acute complications, and these studies will continue to add information on long-term sequelae. We would argue that the use of standard chemotherapy does not preclude the risk of treatment-related late effects and, in the case of OPGs, the unknowing of long-term toxicities is balanced against the potential positive impact on disease-related morbidity. The onus remains on the pediatric neuro-oncologist to inform patients and families not only of possible known long-term toxicities, but of the larger unknown, as providers do with any therapy recommendation.[45]

In summation, choosing the correct targeted Ras pathway inhibitor for our patient over conventional chemotherapy will carry a higher likelihood of vision stabilization, more-tolerable toxicities, decreased clinic visits, decreased intravenous access, and overall better quality of life.

Pro–Chemotherapy Reply (Drs Yeo, Haas-Kogan, and Chi)

The argument for cytotoxic chemotherapy vs targeted therapy for the upfront treatment of a child with an LGG (such as optic pathway pilocytic astrocytoma) can be succinctly summarized as established conventional therapy vs the potential of personalized novel therapeutics. There is little doubt that targeted therapies, along with other forms of personalized therapy, such as cellular and

immunotherapeutics, represent an essential part of the future of cancer treatment. These therapies are already poised to surpass more conventional therapies (chemotherapy, radiation therapy) as the initial treatment of choice for several malignancies, for example, melanoma. However, as it relates specifically to the upfront treatment of a child with a progressive KIAA1549-BRAF–activated optic pathway pilocytic astrocytoma, there is little evidence currently to suggest that targeted therapy with an Ras pathway inhibitor, such as a MEK inhibitor, is superior in efficacy and tolerability when compared with established chemotherapeutic regimens.

We appreciate the thoughtful arguments made by the team from University of California San Francisco. Though conventional chemotherapeutic regimens are associated with several substantial side effects—namely, myelosuppression, risk for infections, and central line complications—these are successfully managed with readily available supportive care protocols (fever/ neutropenia management guidelines, central line care protocols, safe transfusion of blood products, etc). Additionally, although hypersensitivity reactions to carboplatin are common, the availability of effective premedication and desensitization protocols allows for continued usage of this agent in many cases. In the subset of cases in which persistent hypersensitivity precludes its use, there are numerous well-recognized alternative chemotherapy regimens that are equally efficacious.

With regard to vision loss associated with OPGs, we agree there is a paucity of neuro-ophthalmologic outcomes reported in the literature. Although the systematic review by Moreno and colleagues[13] showed that less than 15% of patients experienced improvement of visual function with chemotherapy, the majority of patients reviewed in that paper showed stabilization of visual function. With the lack of a better alternative treatment and the permanent nature of optic nerve damage, stabilization of visual function is widely considered a key goal of therapy.

Despite their therapeutic potential, Ras pathway inhibitors are associated with significant toxicities, undetermined long-term side effects, unproven efficacy, and unknown neuro-ophthalmologic outcomes in patients with OPGs. Therefore, until more data for Ras pathway inhibitors emerge from pediatric clinical trials, we believe that the use of conventional chemotherapy in this patient comes with manageable toxicity with a high likelihood of benefit (stabilization) to her vision and should therefore be the recommended upfront treatment.

Conclusion

Although the case presented was that of one unique clinical scenario, in one disease subtype among many that are called "low-grade glioma," it is indeed illustrative of the complexity of the discussion of risks and benefits when choosing initial treatment approaches for children with these tumors. While encouraging that so many options exist, often with years of disease control, the fact remains that these tumors often recur, present in children in many age groups, during critical neurological and physical development, in multiple areas of the brain and spinal cord, with years of life left for each child. The choice of treatment could potentially affect the quality of survival of the majority of patients who will survive to adulthood. Unfortunately, not all children will survive, and the use of the term "low-grade" is perhaps inappropriate in that context, as well as within the important caveats discussed above of potential toxicity relative to benefit of targeted vs cytotoxic therapy. It is interesting that the initial strategies discussed include agents intended to "kill" tumor cells in a less-selective manner vs targeting specific altered pathways, in an either-or debate. Neither approach is totally effective (curative) in the short term, and many children are treated with both strategies over time. Current trials do not require any assessment of drug/target engagement, or even drug distribution in tumor (enhancing or nonenhancing regions). Whereas toxicity is easier to measure, at least in the short term, efficacy is more problematic. When to treat, based on what biology, with what approach, and for how long, at what toxicity costs are still not resolved. It seems very clear that what is needed are rigorously designed, adequately powered, prospectively controlled clinical trials, within homogenously defined patient subgroups, using agreed on endpoints relative to those patient populations. Clinical trials should be comparable across studies, particularly as they relate to entry inclusion/exclusion requirements, uniform definitions of clinically meaningful benefit, longitudinally evaluated quality of life measures, acute and late effects assessments, neurological functional change over time, with centrally reviewed imaging using guidelines that can be used in multi-institutional settings. The latter critical imaging issue is currently being addressed by a Radiological Assessment in Pediatric Neuro-Oncology committee. Therapy strategies relevant to LGGs in children will not be resolved unless adequately tested in good clinical trials with primary functional endpoints such as visual function, which is currently planned for the European LOGGIC trial. Thus, the current debate: We have many options, with more to come from our immunology colleagues, but few answers. There are many reasons for this dilemma, including an explosion of new biology, multiple agents to target multiple pathway alterations, many strategies to consider, a rare patient population, costs, and a lack of consensus concerning trial design, among others. Fortunately, upcoming trials will soon address some of these critical questions, including SIOP and Children's Oncology Group (COG) studies comparing standard vs targeted treatment, studies proposed and in development by the COG combining targeted and cytotoxic therapy, and others. Physicians always consider risk and benefit when deciding treatment options, and physicians must additionally consider cost. We acknowledge access to therapies is not uniform, and medical decision making often includes logistical and practical concerns. For children with LGG, it seems clear we need more information.

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