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Letter to the Editor

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

We congratulate the editors and authors on their selection and presentation of this informative debate[1] focused on how treatment in the modern molecular era should be selected for a 10-year-old girl, who presents with symptoms of increased intracranial pressure and a unilateral visual defect due to hypothalamic optic nerve glioma, not associated with neurofibromatosis type 1 (NF1). Surgical cyst decompression permitted a biopsy and apparently relieved increased intracranial pressure. Histology revealed a pilocytic astrocytoma with the *BRAF* activation fusion (KIAA 1549-BRAF). Subsequent observation identified both enlargement of solid component of the tumor and visual deterioration.

The authors have fluently assembled the arguments for, and against, molecularly targeted therapy and conventional chemotherapy, while highlighting the almost total lack of evidence in the literature for the impact of any therapy on visual outcome. The current trials will hopefully fill this gap. However, we would like to share our perspective as clinical researchers who have recruited patients to clinical trials and developed a consensus on methods of reporting visual outcomes and factors that influence the selection of those to "treat" vs "observe" in a European research workshop concerned with optic pathway glioma associated with NF1.[2]

The clinical evidence, in this case, justifying consideration of therapy does not include visual or tumor measurements quantified in line with existing eligibility criteria for current clinical trials. Our workshop proposed standardization of the way tumor progression and visual loss is assessed to assist with predicting the threat to vision. Furthermore, it recognized that in childhood, the sensitivity of visual measurements to detect change alters with maturation, constraining the capacity to detect change and therefore predict visual benefits of the different treatment options (see Figure 1B in [2]).

Consideration of detailed visual assessments raises the question of how much vision loss justifies either type of therapy with its side effects. Furthermore, the third option of no therapy was not considered by the authors of the debate. We suggest that the nature of vision loss and its impact on quality of life as judged by detailed radiological and ophthalmic assessment would provide better evidence on which to base treatment decisions. No therapy is associated with no side effects of treatment and arguably no changes in risk of survival.

We raise these issues as the European Research Workshop identified visual acuity, using developmentally appropriate methods and subsequent conversion to logarithm of the minimum angle of resolution scale and graphing of the visual acuities onto the World Health Organization visual acuity scale as the optimal method for recording visual function for all ages[3–6] (Figure 1A in [2]).

We note that there has been a fundamental difference in approach to offering therapy to patients with low-grade glioma between Europe and the United States over the past 2 decades. The European trials have been based on standardized strategies for selecting patients for observation vs therapy,[7–9] whereas the US trials have recruited patients after surgery or at progression without indicating the proportion who were observed initially. The poor visual preservation rates in reports quoted by the authors are not explored. There is an undoubted difficulty in using data from cohorts that include patients with severe and irreversible vision loss due to established optic atrophy as well as patients being treated around the time of visual deterioration, when neuronal recovery could be anticipated. The European research workshop cohort identified that those with the most recently observed visual deterioration are more likely to have visual improvement with chemotherapy than those with severe visual deficit but no recent history (Figure 5 in [2]). Furthermore, an international consensus survey demonstrated a significant lack of agreement among expert trialists concerning the type of clinical presentation that justified selection for observation vs treatment. We have proposed that a trial is needed to provide better evidence for such case selection.

Finally, there is no mention of the state of growth or development of this 10-year-old girl. Tumor progression at age 10 years is atypical, as a population-based UK cohort identified age at diagnosis of younger than 5 years as being associated with greatest risk of tumor presentation and progression.[9] It is established that hypothalamic tumors can lead to precocious puberty in girls and coexisting pubertal development with its impact on sex hormones, growth mechanisms, thyroid function, and steroid axis as important factors determining the wellbeing of the patient, during and after therapy. Furthermore, these changes may be playing a part in the peripubertal tumor progression that has been anecdotally reported. It is our belief that this view of the evidence supports the decision for this girl to be offered treatment. The evidence, such as it is, supports the use of chemotherapy because there is no evidence of vision-sparing effect of mitogen-activated protein kinase inhibitors. An additional therapy consideration would be that at age 10 years, proton therapy could save vision with fewer acute side effects and a shorter duration

of therapy, especially if endocrine deficiencies were already in development.[10] Finally, and most important, the view of the individual child and her capacity to be involved in assent and ultimately consent for such decisions should be a central consideration for practitioners. Low-grade glioma of childhood are nonmalignant tumors with the capacity to kill if increased intracranial pressure or severe brain injury occurs. Biologically, however, the vast majority are self-limiting in their natural history with an extremely low risk of malignant transformation.

In conclusion we would favor a vision-history and endocrine-prioritized approach to treatment selection by which children and their families can exercise their right to choose based on the best scientific evidence that can be applied to this situation. In Europe we will be offering molecularly targeted drugs within clinical trials for the foreseeable future.

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SIOPE NF1 OPG Nottingham, UK, Workshop 2014
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