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Pediatric low-grade gliomas: a brave new world

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See the article by Jones et al. on pages 160–173.

Low-grade gliomas (LGGs) of childhood have long been recognized as distinct from those arising in older adolescents and adults, both in their pathological characteristics and in their biological behavior. Although as a group they represent the most common pediatric primary central nervous system (CNS) tumors, they are recognized to consist of several different pathological entities whose clinical course can be further diversified by patient age and sex and tumor location in the CNS, reflecting both brain region biological heterogeneity and differences in therapeutic accessibility (ie, ease of resection). The added complexity of some tumors exhibiting alternating episodes of disease stabilization and indeed tumor shrinkage, followed by repeated bouts of tumor progression, further challenges clinicians who must decide on the most appropriate treatment, the optimal timing of treatment, and the interpretation of treatment responses.[1–3] The recent consensus statement from Jones et al provides a considerable amount of hope that by comprehensively defining the molecular features of this diverse group of diseases we will be better able to rationally design treatment and time its administration.[4] This would apply to all aspects of treatment; surgery, chemotherapy, and if necessary, radiation therapy.

The integration of molecular diagnostics and targeted therapeutics into pediatric LGG care is likely to further highlight the uniqueness of this family of tumors and challenges in their treatment. In contrast to adult LGG, pediatric LGG uncommonly undergoes transformation to higher-grade gliomas, although the precise frequency with which pediatric diffuse LGG and gangliogliomas do undergo such transformation in the absence of irradiation remains unclarified. Thus, we are not most frequently challenged in pediatric LGG to identify molecular targets and matched drugs in order to improve survival. Instead, we are first charged to find these new treatment approaches in the hopes that we can more effectively prevent tumor recurrence, reduce toxicity and provide the means to treat pediatric LGG as a chronic disease without inducing greater injury through treatment than the disease itself. In addition, it is to be hoped that the rapidly expanding molecular information on pediatric LGG reported in the article by Jones et al will provide a mechanism for identifying those few patients at initial diagnosis who are at risk for malignant transformation and the means for early therapeutic intervention to prevent it.

To date, our approach to pediatric LGG management has been primarily driven on empirical grounds, and among the challenges facing us in this "brave new world" is how to integrate our vast clinical experience with pediatric LGG with newly acquired molecular data. If we prematurely embrace the as yet unproven prognostications of specific molecular aberrations, we may be in danger of overtreating some patients. Additionally, there are concerns regarding which specific tests are sufficiently accurate, reproducible, and interpretable to reliably diagnose certain mutations. The following brief case exemplifies this problem[5]:

> An eight-month-old girl was considered to have progressive growth of a tectal glioma, managed 4 months earlier with a third ventriculostomy for acute hydrocephalus. A tiny endoscopic biopsy was obtained and revealed a diffuse astrocytoma with Ki67 of ~1%. H3.3 K27M was reported as present by immunohistochemistry (IHC), the lesion was thus called by one pathologist an anaplastic astrocytoma, and the family was advised to undergo either (a) palliative proton beam irradiation, (b) marrow-ablative chemotherapy with autologous hematopoietic cell rescue, or (c) chemotherapy according to the "Baby POG" regimen.[5] One additional consultation recommended observation, given that tectal gliomas rarely if ever progress and/or transform to high-grade gliomas in infancy, that the significance of identification of H3.3K27M in tectal LGG is unknown, and finally that identification of H3.3K27M by IHC is unreliably interpreted. The child received no additional treatment and remains with a stable tectal lesion now almost 3 years out from initial biopsy.

How we adjudicate clinical decisions when our empirical experience and molecular diagnostics are in apparent

conflict may be a challenge, but it is one we are equipped to face and is likely to highlight nuances in the optimal integration of molecular diagnostics into clinical care in a manner that may be applicable to all brain tumor treatments.

A further contingency in this approach may be the potential for commonly mutated pathways in pediatric LGG like the Ras-Raf–mitogen-activated protein kinase and phosphatidylinositol-3 kinase pathways to affect cognitive development, function, and behavior. As duly noted in the Jones consensus statement, a greater emphasis on the quality of survival, including cognitive function, will be essential when fully evaluating targeted therapeutics for pediatric LGG. This will be especially important if we approach pediatric LGG as a chronic disease with a need for prolonged therapy. Cognitive deficits and psychiatric disorders are well documented in the RASopathies including neurofibromatosis type 1.[6] Similarly, germline mutations in phosphatase and tensin homolog are associated with autism spectrum disorders,[7] and mammalian target of rapamycin inhibition with everolimus has pleiotropic effects on cognition and mental health.[8] Thus, we can expect that targeted inhibition of these pathways is likely to affect cognitive development, function, and behavior. There is a chance that these drugs will improve these functions, but regardless, we will need to rigorously characterize the effects and, over time, their long-term consequences.

Finally, the biggest challenge of all may be the extension of molecular diagnostics and therapeutic technologies to the world population at large. How the leaders in the major medical centers in which these discoveries are made and new therapies are developed provide guidance to the rest of the world about how to navigate the nuanced landscape of molecular diagnostics and targeted therapeutics will be as important as the advancements themselves. As with the management of all cancers, the timely and reliable application of the tools required to identify actionable mutations, let alone the therapeutic implementation of molecularly targeted therapeutics, will likely be confined to the 15% of patients who reside in the high-income countries of the world. We will need to work with the same commitment and zeal that produced this brave new world to make sure that every child and family can benefit.

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