Past and future challenges for the clinical care of children with low-grade gliomas

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Background

Pediatric low-grade gliomas (PLGG) constitute the most common group of pediatric brain tumors and are histologically heterogeneous. These tumors exhibit rare malignant transformation and relatively slow growth, however, PLGGs can pose great morbidity including neurological dysfunction, endocrinopathies and vascular pathology depending on tumor location as well as the chosen therapeutic approach. The majority of PLGGs can be surgically resected resulting in an excellent 10-year overall survival rate. If complete surgical resection is impossible, PLGG can be viewed as a chronic disease and children often remain on therapy for many years. Due to the known side effects of radiation therapy, most neuro-oncologists favor a chemotherapy approach despite that conventional radiotherapy is a more efficacious method of long-term tumor control. Multiple chemotherapy regimens have been evaluated over the past few decades with comparable survival outcomes but differing toxicity profiles. The ideal therapy for these children however would carry limited side effects with long-term use. In the past, the clinical approach to PLGG was based on a “one size fits all approach.” With the recent advancements in our understanding of the biology of these PLGGs, the goal will be to establish a rational therapy plan based on the underlying genetic makeup of the tumor. This approach is slowly being integrated into the clinic care for these children and the future challenges for the treatment of PLGG will be to decide on combination therapies, duration of therapy and to monitor long-term side effects of these targeted therapies on the developing brain.

Discussion

Classification and molecular aberrations in PLGG

PLGGs account for the majority of pediatric brain tumors and are classified by the current World Health Organization into grade 1 and grade 2 tumors with pilocytic astrocytoma (PA) being the most common subtype. A variety of other less common subtypes is also seen in children, including fibrillary astrocytomas (grade 2), pleomorphic xanthoastrocytoma (PXA), subependymal giant cell astrocytoma (SEGA), and other neuronal and mixed neuronal-glial tumors such as gangliogliomas. Despite these numerous categories, a significant percentage of PLGGs cannot be classified based on the current WHO criteria. This poses a significant challenge for the treating physician as well as for the interpretation of clinical trial results for any given subtype. Recent discoveries have shed light into the molecular underpinnings of PLGGs and the challenge remains how these molecular aberrations will be integrated into the current WHO-based classification scheme for PLGGs and clinical trial enrollment.
Alterations affecting the BRAF oncogene resulting in activation of the mitogen-activated protein kinase (MAPK) pathway seem to be the most important signaling pathway in these tumors. In sporadic PLGGs, BRAF alterations leading to MAPK pathway activation are most commonly implicated. BRAF is one of the three members of the Raf kinase family and is a key regulator of the MAPK pathway. In the majority of PAs (53 percent–72 percent), BRAF is activated through formation of the KIAA1549:BRAF fusion protein, which leads to constitutively activation of the kinase (1–3). The most common point mutation in pediatric LGGs is the BRAF V600E mutation leading also to constitutive activation of the MAPK pathway (4–6). This mutation is found in 9 percent of PAs, 18 percent of grade 2 astrocytomas, 69 percent of PXAs and 13–50 percent of gangliogliomas (4–6). Whole genome sequencing has identified single somatic mutations and new fusion proteins affecting the MAPK pathway (7, 8). These studies establish MAPK alterations as a hallmark of PLGGs, with BRAF mutations as likely genetic driver events in discrete histological subclasses that can be exploited for therapy. Further activation of the PI3K/mTOR pathway plays a central role in PLGG pathogenesis (9, 10). Published studies document PI3K/mTOR activation in approximately 50 percent of PLGGs (9, 10).

**Surgery**

Surgery remains the mainstay of therapy for children with PLGGs. Gross total resection often leads to excellent long-term clinical outcomes and is often curative for children with PAs. Recent analyses from a large cohort of children (n = 4,040) have questioned the benefit of aggressive surgical resections, specifically if these are leading to long-term neurological deficits. This study showed that children with GTR versus children with residual disease had no significant difference in overall survival (11). The feasibility of an open-surgical approach depends upon several factors, the most important being tumor location. PLGGs located within midline locations such as optic pathway/hypothalamus, thalamus, and brainstem are usually not amenable to open surgical resection and stereotactic biopsies are often performed to establish a histological diagnosis. At time of progression the majority of patients do not undergo subsequent surgeries, which limits our ability to assess molecular changes and potential mechanisms of resistance to the initial therapy. Specifically with the integration of targeted therapies this needs to be reconsidered so that rational combination therapies can be developed.

**Current chemotherapy approaches**

To avoid the significant morbidity associated with radiation therapy, most pediatric neuro-oncologists will use chemotherapy as a first-line treatment for midline and for progressive/recurrent tumors if surgery is not feasible. Over the past few decades, multiple chemotherapy agents have been used in the treatment of newly diagnosed and progressive/recurrent LGGs. The current standard of care is still considered to be a combination of carboplatin and vincristine based on one of the largest PLGG studies conducted to date. This trial randomized 274 PLGGs to receive carboplatin and vincristine (CV) versus thioguanine, procarbazine, lomustine, and vincristine (TPCV). The five-year EFS rates were 39 ± 4 percent for CV and 52 ± 5 percent for TPCV. However, this difference in EFS was not statistically significant and
the TPCV regimen was associated with increased toxicity (12). Other agents that have been explored include vinblastine, temozolomide, bevacizumab and irinotecan, cisplatin, and etoposide resulting in EFS ranging from 34 percent to 78 percent (reviewed in (13).

**Future Directions for PLGG**

With our increased understanding of the molecular underpinnings of PLGGs and available inhibitors, targeted therapies are slowly entering the clinic.

**mTOR inhibition**

Recent clinical trials have demonstrated promising results for mTOR inhibition. However, biomarkers to predict response to such therapy are missing. Copious evidence indicates, however, that molecular markers will define subgroups of PLGGs that are more likely to respond to everolimus. An ongoing trial conducted by the Pacific Pediatric Neuro-Oncology Consortium (PNOC) is currently testing everolimus for the treatment of recurrent PLGGs. This trial mandates tissue from each enrolled child, and thus provides the tools and tissues to assess determinants of response to everolimus. Specifically, this trial will answer the question if evidence of PI3K pathway activation is indicative of response to therapy with mTOR inhibition, which is critical for the next generation of clinical trials.

**MEK inhibition**

Currently several MEK inhibitors are being tested in clinical trials. The most advanced in the pediatric population is selumetinib. In a phase I study conducted by the Pediatric Brain Tumor Consortium (PBTC), eight of 38 children who received selumetinib for progressive PLGGs responded (one complete, seven partial). Of these, five had biology data: 3 KIAA1549:BRAF, 1 BRAFV600E and 1 negative for both (14). On ongoing phase II study will assess the activity of this agent in a variety of different PLGGs. Other MEK inhibitors include trametinib as well as MEK162. Ongoing phase I studies will test the safety and tolerability of these agents in PLGGs and correlate clinical outcome with BRAF status.

**BRAFV600 inhibition**

There are now several BRAFV600E specific inhibitors in clinic and individual case reports are encouraging regarding the clinical activity in BRAFV600E mutated gliomas (15–17). The PNOC is currently conducting a phase I clinical trial of specific BRAFV600E inhibitor vemurafenib in children with BRAFV600E mutated gliomas. In a recent study of patients with BRAFV600E mutated melanoma, BRAFV600 inhibition led to an initial response in the majority of patients but within six to nine months, tumors progressed and developed different escape mechanisms (18). In order to avoid development of such resistance, combination treatment strategies have to be developed.

With the introduction of targeted therapies for PLGGs it will be critical to determine biomarkers for treatment response and assess mechanism of resistance for single agent therapy. Further, attention needs to be paid to the effect of these targeted agents on the long-term health of these children with a specific focus on the developing brain.
Pediatric Low-grade Gliomas: Silent but Still Deadly

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