

Evolution in the Management of Childhood Low-Grade Gliomas and Neuronal/Mixed Neuronal-Glial Tumors

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Gliomas comprise the majority of tumors occurring in those less than 18 years of age and unlike the situation in adulthood, the majority of pediatric gliomas are low-grade. Since demonstration of the benefits of chemotherapy by multiple single-arm and randomized prospective studies, there has been a shift in management of unresectable, progressive low-grade gliomas (LGGs) from initial treatment with radiation therapy to the employment of chemotherapy in attempts to delay and in some cases obviate the need for radiation therapy or potentially damaging «definitive» surgery [1, 2]. A variety of different chemo-therapeutic approaches have been utilized, most attempting to use relatively non-mutagenic agents such as the combination of carboplatin and vincristine, carboplatin alone or vinblastine alone [1, 2].

Although such therapies are successful in delaying the need for radiation therapy or other interventions in 80% or more patients with LGGs while on treatment or during the first 1–2 years off treatment, 5-year progression-free survival rates for children with sporadic LGGs after treatment with chemotherapy are only 30–40% [1, 2]. The degree of disease control is better in patients with NF1, as children with NF1-associated pilocytic astrocytomas (PAs) have approximately a 70% 5 years progression-free survival after treatment with chemotherapy [1, 2]. The benefits of chemotherapy as regards functional improvements are less well documented and the majority of patients do not clinically improve after treatment [1–3]. This is especially true for children with tumors of the visual pathway [3]. Also, for many patients with LGGs, because of the tendency of these tumors to relapse within the first 5 years after treatment, patients may cycle from one form of chemotherapy to another or ultimately receive

radiation therapy in attempts to gain longer term tumor control.

For those children with the closely aligned neuronal and mixed neuronal glial tumors, approaches to treatment are even less straightforward. Lesions such as gangliogliomas (GGs) and dysembryoplastic neuroepithelial tumors (DNETs) often present with seizures. The mainstay of treatment is surgery and complete surgical removal results in excellent long-term control and often complete cessation of seizures. However, in those tumors in eloquent regions of brain not amenable to complete or near total resections, management is less straightforward. Many tumors seem to remain quiescent for years, while others slowly progressed with suboptimal seizure control. Given the benign nature of these tumors, there is reluctance to utilize radiotherapy unless the tumor had anaplastic features. The relative rarity of progressive GGs, DNETs, or other neuro-glial low-grade tumors makes prospective clinical trials difficult to mount and the benefits of chemotherapy as regards tumor control or control of symptomatology are very unclear.

Introduction of Molecular-Targeted Therapies

The therapeutic landscape for pediatric LGGs and mixed neuronal glial tumors has dramatically and rapidly evolved over the past two decades, especially in the last 10 years. Approaches that were introduced 15–20 years ago included the use of mTOR inhibitors and antiangiogenic agents. The mTOR inhibitor rapamycin was shown to have dramatic benefits for patients with tuberous sclerosis and giant cell astrocytomas; demonstrable tumor shrinkage was noted in the majority of patients, which was durable as long as the medication was maintained [4, 5]. Rapamycin

treatment also resulted in clinical benefit for patients, including, in some, improved seizure control [6, 7]. A second generation mTOR inhibitor everolimus (RAD001), has also benefited some patients with sporadic and NF1-associated PAs and possibly other LGGs [8]. However, the objective response rate to everolimus (RAD001) is only approximately 20%, with the majority of responding patients having stable disease on treatment [8].

Bevacizumab, an antiangiogenic agent, was first utilized for progressive LGGs, including PAs, in the late 1990s. The drug either used singly or in combination with irinotecan resulted in objective radiographic responses in 50% or more of tumors [9, 10]. Probably even more importantly, treatment resulted in clinical improvement, including visual improvement in some patients, who had failed «standard» chemotherapy and/or radiotherapy [9, 11]. Dramatic recovery of vision, including acuity and visual field, was seen after relatively long-standing dysfunction [11]. Bevacizumab remains an important part of the armamentarium for patients with recurrent PAs, especially those with acute neurologic or visual deterioration. However, many patients lose disease control when stopping the drug. Given the potential of severe side effects including hemorrhage, blood clotting and kidney damage, as well as more common side effects such as hypertension and proteinuria, long-term use of bevacizumab can be problematic. Dose schedules extending the duration between treatments from 2 to 3 weeks and reducing dose per treatment (one-half dose) have been occasionally successful in allowing longer term treatment. A prospective trial is ongoing in newly diagnosed patients with progressive LGGs randomizing between treatment with vinblastine alone and bevacizumab and vinblastine with the bevacizumab being utilized for the first six months of treatment. This trial is not only assessing disease control but clinical, especially visual, outcomes.

Inhibitors of the RAS-MAPK Pathway

However, the greatest enthusiasm for the alternative treatment of LGGs has been engendered by early results of the use of inhibitors which directly inhibit the RAS-MAPK signaling pathway. Ground breaking work by multiple researchers has demonstrated that at least 80%, if not a higher percentage of children with sporadic PAs, have a demonstrable mutation in the RAS-MAPK pathway, the most common of which are either a BRAF activating fusion or a V600E mutation [12, 13]. Other mutations, including other activating BRAF fusions, FGFR1 mutations [13], NTRK fusions and mutations have been discovered in the signaling pathway underlying sporadic PAs and other LGGs [14]. NF1-associated PAs have NF1 loss and resultant in

aberrant RAS-MAPK signaling [15]. BRAF V600E mutations have been identified in some apparent PAs but also in diffuse LGGs and increasingly in the neuronal and mixed neuronal glial tumors, such as GGs and pleomorphic xanthoastrocytomas [12, 13]. Soon after these discoveries, both the MEK inhibitors and the BRAF V600E mutation inhibitors were employed and have been remarkably effective in appropriate molecular subsets of patients with LGGs who have failed standard form of therapies.

Selumetinib was the first MEK inhibitor widely tested and has demonstrated activity in both BRAF fusion and V600E mutated LGGs [16]. Some degree of radiographic response was seen in approximately 70% of sporadic BRAF-fusion LGGs and nearly 40% had greater than a 50% shrinkage of tumor. The results were even more impressive in patients with NF1-related progressive PAs, as some degree of radiographic response was seen in over 90% and a 50% reduction seen in 40–50% of patients [17]. Anecdotally, some patients responding to treatment also had clinical improvement, although this information was not well gathered by the largest prospective study done to date. Other MEK inhibitors have been tested, such as trametinib and binimetinib and early results have also been favorable [18, 19]; trials are ongoing and definitive reporting of results is pending.

For those tumors with BRAF V600E mutations both dabrafenib and vemurafenib have been tested. The results of dabrafenib and vemurafenib therapeutic trials have not yet been fully reported, but abstracts and case reports have demonstrated frequent benefit [20, 21]. The selumetinib phase I trial also showed benefit for children with sporadic V600E mutated LGGs. In contradistinction, the V600E inhibitor sorafenib demonstrated a paradoxical effect, with increased tumor growth in sporadic BRAF-fusion and NF1-associated PAs; this highlights the need for biopsy and molecular study to determine the presence of and type of mutation in the tumor [22].

All this information has generated tremendous interest in both the patient and physician community and calls for utilizing these drugs earlier in the course of illness, not only for PAs or diffuse LGGs, but also in the mixed neuronal glial tumors where there is little prospective information demonstrating the benefits of chemotherapy. However, some limitations must be acknowledged concerning these new therapeutic options. The RAS-MAPK pathway is a critical pathway in development and the impacts of inhibitor treatment, especially in young children as regards brain development, neurologic function and for that matter, other organs' development and function are unclear. These inhibitors have different toxicities than those that generally occur with chemotherapy.

Bone marrow toxicity is relatively infrequent, but rash which can be severe, especially in pubertal patients (with the MEK inhibitors), skin cancer (with the V600E inhibitors) may occur. The development of the MEK inhibitors was initially slowed by the infrequent, but potentially devastating occurrence of retinal venous occlusion, which can result in irreversible visual loss. This visual risk, although rare, is of significant concern in all of patients receiving this class of drug and is especially problematic in children with visual pathway tumors and already impaired vision. The durability of response of both MEK and V600E inhibitors is also just being clarified [17]. The impact of these drugs on senescence, a mechanism by which these low-grade tumors seem, in many cases to, eventually turn themselves off in older childhood and adolescence is unknown. Also the relative benefit of these drugs compared to that of chemotherapy in newly-diagnosed patients has never been evaluated. Adding to the complexity of MEK-inhibitor use is that there are multiple MEK inhibitors presently either available or in testing and the relative value of one compared to another as regards disease control, durability of response and tolerance of side effects is unknown. As effective as MEK and V600E inhibitors are, other selective agents, including those inhibiting NTRK, FGFR1 and other mutations are now in trial and are likely more effective in the correct biologic subtype.

Even with all of these cautions, there seems to be little question that these and other drugs which dampen signaling through the RAS-MAPK signaling pathway are a potential great advance for the treatment of LGGs and low-grade mixed neuronal glial tumors. Randomized prospective trials are underway in children with NF1-associated LGGs and are soon to open in children with sporadic LGGs, comparing chemotherapy with carboplatin and vincristine to selumetinib through the Children's Oncology Group. Studies are also underway evaluating dabrafenib in

newly diagnosed patients with LGGs which are driven by V600E mutations. Given the potential benefits of these drugs and also their potential toxicities (some of which may not even be known at the present time), it is of utmost importance for these trials to be completed before these drugs are routinely utilized in treatment naive patient. Such trials should measure not only the radiographic benefit of these new agents, but also their impact on neurologic function and in those with visual pathway tumors, visual function.

Other studies are underway in children and adults with low-grade tumors coupling these drugs with chemotherapy or other molecular-targeted therapies in attempts to increase the frequency of and to prolong duration of response. It will likely essentially become mandatory for patients with sporadic low-grade tumors to have the tumor tissue assessed molecularly to determine the type of mutation present, so as to best guide therapy. Even in those with NF1, given the new data that some older children and adults may have not only tumor NF1 mutation but other concomitant mutations, such as CDKN2A and ATRX mutations, biopsy is likely to play an increasing role [15, 23].

There is no question that the treatment of pediatric LGGs and low-grade neuroglial tumors is rapidly evolving and the armamentarium of potential treatments is growing rapidly. Harnessing this new knowledge and reaping the potential benefits of these new therapies are an exciting and an ongoing challenge.

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CONFLICT OF INTEREST

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