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Tumors of Brain in Kids: Current Insights from Biology and Plans for Future

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Abstract

Sadly, many subtypes of brain tumors continue to have poor long-term outcomes, making them the most common solid tumor in children. High-resolution genomic, epigenetic, and transcriptomic profiling, on the other hand, has made remarkable inroads into our comprehension of the molecular underpinnings of these tumors over the past few years. These insights have led to improved tumor categorization and molecularly directed therapies. Medulloblastomas, for example, have historically been classified as either standard-risk or high-risk, but it is now known that these tumors are made up of four or more distinct molecular subsets with distinct clinical and molecular characteristics. Similarly, it is now known that high-grade glioma, which was previously thought to be a single high-risk entity for decades, consists of multiple subsets of tumors with varying patient age, tumor location, and prognosis. For ependymal, which has at least nine distinct subtypes of tumors, the situation is even more complicated. On the other hand, it appears that the majority of Pilocytic Astrocytoma is caused by genetic changes that alter a single molecular pathway that can be targeted for treatment.

Keywords: Brain • Tumor • Medulloblastoma • Glioma • Polycystic • Astrocytoma

Introduction

Though advances in surgical and adjuvant treatment have increased the survival rates of children with cancer, brain tumors still account for the majority of childhood cancer deaths. Medulloblastoma and Low Grade Glioma (LGG), for which 5-year survival rates now exceed 75% the prognosis for other tumors like Diffuse Intrinsic Pontine Glioma (DIPG) and other Midline High Grade Gliomas (HGGs) remains poor. Additionally, as survival rates for children with prognostically favorable tumors have improved, there is growing concerns that "cure" frequently. As a result, novel treatment strategies have been used to try to increase cure rates in tumors with poor risk, while risk-adapted treatment protocols have been used to reduce the morbidity of therapy for tumors with favorable risk [1].

Discussion

Perspectives on the molecular level, the status quo, and the path forward

While BRAF mutations are more prevalent in gangliogliomas, Pleomorphic Xanthoastrocytomas, and Cerebral Pilocytic Astrocytomas, BRAF-KIAA fusions are common in optic pathway pilocytic tumors and cerebellar and optic pathway pilocytic tumors. Other components of the Mitogen-Activated Protein Kinase (MAPK) signaling pathway, such as NF1 mutations and RAF fusions, are frequently altered in tumors devoid of BRAF mutations or fusions. Targeted inhibition of MAPK signaling as a treatment for these tumors was sparked by the convergence of mutations on a single downstream pathway. Selumetinib2 and other agents that block MEK1/2 (MAPK/ERK kinase) have shown promising initial results in recent research. A phase II study of this agent was launched, stratifying patients according to MAPK pathway mutation status (e.g. BRAF translocations or mutations), histological diagnosis, and presence of NF1. Based on these results, a phase II study of this agent was launched, stratifying patients according to MAPK pathway mutation status (e.g., BRAF translocations or mutations) [3, 4].

Patients with WNT-activated medulloblastoma have an excellent prognosis when treated with standard doses of craniospinal RT and chemotherapy following surgery. Therefore, at

least four multi institutional clinical trials are currently evaluating the PFS of patients with newly diagnosed non-metastatic WNT-activated medulloblastoma treated using no or reduced doses of craniospinal RT at 18 Gy (COG ACNS142 and SIOP PNET5), 15 Gy (SJMB12), and chemotherapy that is less intense (COG ACNS1422 and SIOP PNET5). To avoid including patients with high-risk characteristics (such as large cell/anaplastic histology, MYC or MYCN amplification, etc.), all studies have stringent eligibility requirements and only include patients who have at least two of the three positive markers that were mentioned earlier [5].

A recent integrated genomic analysis of 1000 pediatric HGGs and DIPGs37 has given the aforementioned classification some texture. It has brought to light the existence of recurrent genomic anomalies within the aforementioned subgroups, which may help refine subgroup classifications further. These data, taken as a whole, highlight the genomic and prognostic diversity of these tumors, provide insights for therapeutic risk grouping of patients, and suggest therapeutic molecular targets [6, 7].

Due to their high prevalence of K27 mutations, histone deacetylase (HDAC) inhibitors have been used in DIPGs to target the K27M mutation in this context. Panobinostat, an HDAC inhibitor that has been shown to be effective in DIPG preclinical models, is currently being studied by the PBTC.19 COG studies of BRAFV600E and MAPK inhibition with dabrafenib and trametinib are also being developed for the subset of HGGs that have BRAF mutations. A protocol using ABT888, a poly (ADP-ribose) (PARP) inhibitor, as a radio sensitizer is being developed for the subsets of tumors without IDH, K27, or BRAF mutations [8].

Conclusion

For children with a variety of brain tumors, advances in neuroimaging, surgical technology, conformal RT delivery, and conventional chemotherapy have improved outcomes. Recent advancements in the molecular characterization of virtually every kind of childhood brain tumor have added to the improvement of these modalities. New classes of molecularly targeted therapeutic agents and risk-adapted treatment stratification have emerged as a result of this. These insights are already having an impact on the range of LGGs' first-line treatment options; however, drug development has not kept up with the discovery of new molecular targets, so progress has been slower for other types of tumor. Although the molecular heterogeneity of the majority of high-grade tumors and their propensity to develop resistance to initially effective therapies will remain a challenge, this situation is likely to improve over time as new agents are developed [9, 10].

Conflict of Interests

None

Acknowledgments

None

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