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COMMENTARY OPEN ACCESS

Early-Phase Research in Pediatric Neuro-Oncology

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Pediatric brain tumors remain the most common form of solid tumors in children [1]. While there have been great strides made regarding treatment in the last decades, childhood central nervous system (CNS) tumors—particularly high-grade gliomas—remain the deadliest form of pediatric cancer [2]. With modern medical advances in molecular profiling, there has been an increased interest in understanding the genetic drivers for cancer growth and how treatments can be tailored to each patient's specific mutation profile. As within the larger field of oncology, shifts toward targeted therapies, immunotherapies, and cellular therapies have been of interest in advancing treatment in pediatric neuro-oncology. Here are discussed some of the challenges and notable updates in early-phase studies for pediatric brain tumors.

There are various obstacles in the pursuit of early-phase pediatric brain tumor research, some of which are common to pediatric oncology and others that are specific to pediatric neuro-oncology. First, these populations are very small, making it challenging to recruit and validly study new therapies. Likewise, preclinical research based on adult tumor models may not directly translate to the pediatric population. With both the small cohorts and diversity of tumor pathologies and genetic subtypes, completing comprehensive studies can be difficult [3, 4]. Regarding CNS tumors, drugs must be able to overcome the blood–brain barrier (BBB) to be effective against neurological malignancies [5]. So too, there are symptoms of disease (e.g., cranial nerve deficits, weakness) and toxicities (e.g., seizures, developmental delays) from therapy that make developing and monitoring pediatric brain tumor therapies difficult.

Importantly, conducting early-phase trials in children requires careful monitoring for ongoing safety and long-term impacts on the children's growth and development. Especially as rates of overall survival continue to improve, treatments need to be considered in the light of the effects that they may cause as patients become survivors. On a larger scale, additional limitations with eligibility criteria and coordination between multiple centers can present obstacles [4, 6]. With these barriers come financial and resource constraints, which limit the ability of companies and institutions to invest in researching and developing potential therapies. Pediatric oncology continues to remain an area of increased need for research funding and focus.

Chemotherapy has long been a foundational aspect of cancer care. In the previous decades, numerous agents and combinations have been studied and approved for the diverse array of pediatric brain tumors. Most recently, combinations including irinotecan, bevacizumab, and temozolomide, as well as regimens with histone deacetylase inhibitors (e.g., vorinostat, panobinostat), have been under investigation [4]. While there are not many recent studies researching traditional chemotherapeutic agents, many newer drugs are being investigated in combination with standard regimens to build off of already established standards, aiming to improve outcomes and tailor treatments to patients' specific tumor type, molecular profile, and so forth.

In the move toward more specialized treatments, there are several oral medications to target specific genetic mutations that have been approved in recent years. Among them are dabrafenib and tovorafenib for BRAF alterations, trametinib and selumetinib for MEK pathways, and vorasidenib for IDH1/2 mutations [6]. These medications have had significant success in treating tumors harboring variations in these genes. They have provided a helpful modality to be used as monotherapy and in combination with standard therapies. Another exciting recent approval was of dordaviprone, a drug found to have an effect in recurrent diffuse midline glioma (DMG) with an H3K27M mutation, one of the

deadliest pediatric brain tumors [7]. Though the prognosis for these patients remains poor, this new therapy provides another option where they are otherwise limited.

Currently, ongoing early-phase trials regarding targeted therapies include avutometinib (RAF-MEK), tazemetostat (SMARCB1/A4), alectinib (ALK), larotrectinib (NTRK), olutasidenib (IDH1), palbociclib (CDK4/6), erlotinib (EGFR), adavosertib (WEE1), among other tyrosine kinase inhibitors (e.g., imatinib and lapatinib) [4, 8–10]. These drugs seek to expand the portfolio of targetable mutations and pathways and to improve upon the side effect profile of existing therapies. Following the approval of dordaviprone for H3K27M-mutant DMG, a similar drug named ONC206 continues to be evaluated in clinical trials [11]. These studies offer insights into the numerous ways in which patients' tumors can be targeted beyond standard chemotherapy.

Radiation therapy is another widely used modality for treating pediatric brain tumors. While it is effective against a number of tumor types, it comes with the notable risks of neurocognitive impacts (especially in young pediatric patients) and other secondary effects (e.g., endocrinopathies, vision defects, secondary malignancy, etc.). Therefore, the Phase II study ACNS2021 continues in the series of studies investigating reducing the field of radiation in patients with CNS germinoma to maintain efficacy while limiting long-term effects of treatment [12]. In high-grade gliomas, including diffuse intrinsic pontine glioma, radiotherapy is a mainstay of front-line treatment. However, it is often not curative. As such, the Phase I/II study ACNS1821 seeks to evaluate the safety and efficacy of combining selinexor, a histone deacetylase inhibitor, with radiation therapy [13]. As temozolomide has been a long-standing radiosensitizer, other chemotherapies can be considered to provide additional options and benefits for patients.

Immunotherapies have continued to be increasingly considered for treating pediatric brain tumors. While microsatellite instability (characteristic of immunotherapy susceptibility) is rare in this population, when found, it can be a beneficial option [14]. Specifically, high tumor mutation burden also correlates with a higher response to programmed cell death (PD) blockade. Multiple studies investigate combinations of immunotherapies, while others add chemotherapies and targeted therapies in combination with immune checkpoint inhibitors [8–10]. Still others evaluate the role of immunomodulators, such as indoximod, in combination with a variety of chemotherapies and radiation therapy [15]. The role of the tumor microenvironment, how immune cells modulate it, and how drugs can assist in boosting the immune response to pediatric brain tumors is an increasing area of intriguing research.

Novel cellular therapies are also being evaluated in early-phase clinical trials. Chimeric antigen receptor T-cell (CAR T) therapies are being studied, primarily in patients with DMG and progressive/recurrent malignant pediatric brain tumors. Targets for the CAR T treatments include GD2, HER2, B7-H3, EGFR, and IL13Ra2 [16]. Other modalities of cellular therapies under investigation include viral vaccine (e.g., G207, M032, PEP-CMV) and natural killer (NK) cell infusions [10, 17–19]. All of these trials require infusion into the tumor bed or into the CNS, via catheter or Ommaya port, to overcome the difficulty of crossing the BBB. These treatments provide opportunities to adapt novel cellular therapy modalities being researched in adult and other oncologic specialties to the pediatric neuro-oncology field.

Due to the diversity and aggressiveness of many pediatric brain tumors, the field remains an area of continued need for development of new, safe, and effective therapies. There are various challenges researchers face in both pediatrics and neuro-oncology. As advances continue to specialize treatments and improve outcomes, investigation of the long-term effects of therapies remains integral to these efforts. With the approval of targeted therapies that have continued over the past decades, the newer approaches of immunotherapies and cellular therapies offer intriguing opportunities for ongoing early-phase clinical trials. Looking back on past decades, it is hopeful to imagine what milestones will be achieved in the upcoming years.

Conflicts of Interest

The author declares no conflicts of interest.

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