Sri Gururangan and Henry Friedman present a thoughtful review of advances in pediatric neurooncology. Coupled with the recent review of pediatric brain tumor biology written by Richard Gilbertson, these articles highlight the value that the pediatric neuro-oncology community places on translating signal transduction modifiers into clinical practice.[1] The remainder of this commentary focuses on the challenges and opportunities associated with developing more effective and less toxic therapies for children with brain tumors.

Over the past 30 years, the cure rate for children with all types of malignant cancer has improved from less than 15% to more than 75%. Improvement for children with malignant brain cancer has been more limited. Gururangan and Friedman point out the limitations of surgical and radiotherapeutic approaches for tumors surrounded by precious, developing brain and the limitations of chemotherapy caused by the blood-brain barrier and intrinsic resistance mechanisms. Additional obstacles include insufficient biologic material and appropriate models for studying the diseases as well as the relatively small number of patients available for participation in clinical trials.

Biologic Materials and Models

In the past, the relatively low incidence of pediatric brain tumors limited the quality of data generated in single-institution studies. The Cooperative Human Tissue Network (CHTN) addressed this problem by developing a national tumor bank that has steadily accrued specimens and provided them to researchers (www.chtn.ims.nci.nih.gov). Unfortunately, the size of specimens provided to CHTN is typically < 50 mg, which severely limits the number of studies that can be conducted. Given that the average pediatric brain tumor weighs approximately 13 g at diagnosis, this represents only 0.3% of surgical material. In a small number of centers, surgeons and pathologists now provide gram quantities of tumor material for research, demonstrating the feasibility and safety of providing adequate samples.

There are no cell lines or mouse models for most types of pediatric brain cancer. A small number of medulloblastoma cell lines and xenograft models exist, but laboratory subculturing selects for cells that differ markedly from patient material. A genetically precise medulloblastoma model was developed in Matt Scott's laboratory by targeted disruption of the patched gene, a negative regulator of the sonic hedgehog pathway.[2] Although this model has been helpful in understanding medulloblastoma biology, tumors typically arise in only 10% to 15% of animals. This limits the utility of this model for drug testing. Some investigators have generated tumors more rapidly and with higher frequency by crossing the mice onto a p53-deficient background or irradiating young mice. These approaches have been criticized as artificial because p53 mutations are rare in medulloblastoma, and patients have rarely received irradiation prior to diagnosis. A new genetically precise mouse model that activates the hedgehog pathway through constitutively active smoothened (a protein) has recently been reported. These mice have a 48% medulloblastoma incidence with a median age of onset at 25.7 weeks.[3]

The National Cancer Institute Brain Tumor Progress Review Group established the following priorities for pediatric brain tumor research: (1) identify the signaling pathways involved, their relationship to developmental neurobiology, and their implications for new therapy, and (2) use knowledge of tumor phenotype and genetic alterations to generate genetically precise animal models that can be used to...
evaluate and prioritize potential new therapies. Laboratories are actively engaged in these pursuits.

**Accelerating Clinical Trials**

One of the greatest challenges facing investigators in the field of pediatric neuro-oncology is the relative paucity of patients for clinical trials. In the upcoming Children's Oncology Group (COG) study of high-risk medulloblastoma/primitive neuroectodermal tumor (PNET), it will take 5 years to accrue 300 patients. At that rate, it will take over 30 years just to test the classes of compounds that already show promise in preclinical studies. For less common brain tumors, the challenge is amplified. As survival rates improve, even larger cohorts will be needed for appropriate statistical power if clinical trial design fails to evolve. The challenge is to identify new clinical trial end points to rapidly identify treatments that are failing so that other drugs can be tested. In doing so, we will be able to test more agents in individual patients, particularly in phase II trials.

The National Institutes of Health (NIH) roadmap for research may help accelerate clinical trials (nihroadmap.nih.gov). The roadmap establishes molecular imaging and nanomedicine as NIH research priorities. Molecular imaging refers to emerging techniques that enable noninvasive imaging of cell death, enzyme activity, protein interactions, or other molecular events, which have traditionally been measured only in laboratory studies. For example, magnetic resonance imaging contrast agents that bind to cancer cells undergoing cell death may be useful for determining whether an experimental therapy is effective in a matter of days, rather than the current standard of measuring tumor volume every few months. Applying a clinical trial end point that takes days rather than months will enable us to rapidly stop using ineffective agents and optimize effective drug combinations in individual patients.

Nanomedicine—the use of medical therapies, diagnostics, or response indicators that are nanometers in size—likewise has the potential to accelerate clinical investigation. Ideas range from nanoparticles that deliver a "payload" of chemotherapy to tumor cells to nanoarrays that detect genetic mutations in minute quantities of tissue.

Molecular pathology—the determination of whether a drug target is present, absent, or present and mutated by polymerase chain reaction, immunocytochemistry, or other techniques—may also accelerate clinical trials by identifying subsets of patients who are most likely to benefit from a candidate therapy. Eliminating likely nonresponders based on molecular profiles of their tumor samples sharply reduces the number of patients required to statistically detect a drug response. The transition from intensifying chemotherapy to targeting vulnerable signal transduction pathways has been facilitated by the extraordinary infrastructure of the Pediatric Brain Tumor Consortium and the COG. Investigators affiliated with these organizations are actively developing genetically precise animal models, identifying vulnerable signal transduction pathways, and recognizing molecular signatures that are pertinent to drug efficacy. These organizations are poised to embrace new clinical trial end points and designs that enable advances even for uncommon cancers.

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