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Rare central nervous system tumors: the path to progress

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"*This is an exceptional time for cancer research. The NCI is deeply committed to working to advance treatment for rare CNS tumors through NCI-CONNECT by fostering patient-advocacy-provider partnerships.*" (Norman E. Sharpless, MD, Director, NCI)

"*Most brain tumors are considered rare cancers. However, within that category, there are even rarer tumors where outcome for patients continue to remain poor. This supplement focuses on better understanding of their biology, classification, and design of clinical trials. I know that the content offered here will improve our understanding and highlight the gaps where focus should be in research and future clinical trials.*" (Gelareh Zadeh, MD, PhD, President, Society for Neuro-Oncology (SNO))

"*It is an FDA priority to expedite the development of new and safe treatments for people with rare diseases. They [FDA] are committed to addressing the challenges people face with rare CNS tumors and find better treatments and cures.*" (Stephen M. Hahn, MD, former 24th Commissioner of Food and Drugs, U.S. FDA (9/25/2020))

"*A sense of loneliness can follow patients and families impacted by rare CNS tumors. Those feelings highlight the importance of building a strong partnership between patients and physicians.*" (Kimberly Wallgren, Executive Director of the CERN Foundation, a program of the National Brain Tumor Society)

When we envisioned this Supplement to *Neuro-Oncology*, our purpose was not only to increase awareness about the challenges of clinical care and research in rare central nervous system (CNS) tumors but also to outline solutions. Primary CNS tumors are relatively uncommon compared to other oncologic diagnoses but contribute substantially to cancer morbidity and mortality at all ages and especially in children and young adults.[1] Despite the vast unmet need for better treatments, progress in rare CNS cancers has been slow even in recent years as multiple experimental drugs and treatment approaches have reached regulatory approvals for many other more frequent cancers. Meanwhile, even glioblastoma, the most frequent malignant primary brain tumor in adults with an incidence of about 3 new cases for every 100 000 people and more than 13 000 total cases diagnosed per year in the United States, remains incurable with very few treatment options.

Most tumor types are even less common representing less than 10% of all primary CNS tumors. Many of them have an incidence in the United States that falls below 1000 new cases per year in adults. With such low incidence, it is easy to enumerate reasons for this slow progress and resulting lack of well-defined standards of care. These reasons include, but are not limited to, scarce social and advocacy support, an insufficient number of good preclinical models on which to build clinical trials, and the challenges in both providing care and conducting research due to the conundrum of needing to concentrate these activities in centers with expertise. This simultaneously creates an enormous logistical challenge for people with a rare primary CNS tumor diagnosis who need access to such centers for specialized care and may be limited due to barriers including geographic distance, financial constraints, and other factors.

Our supplement reviews essential aspects of basic, translational, and clinical research in rare CNS tumors, including preclinical models, advances in tumor classification and molecular analysis, options for clinical trial design, incorporation of patient outcome measures in clinical care and clinical trials, and current models of multidisciplinary and multicenter collaboration to advance science and care.

In the first manuscript dedicated to preclinical models in rare CNS tumors, Aleena K. S. Arakaki and colleagues

describe available in vitro, ex vivo, and in vivo models to study CNS cancer progression and drug response, and the path from discovery of driving molecular alterations defining new tumor subtypes to the development of preclinical models and ultimately clinical trials, of which RELA fusion ependymoma represents a paradigm. The importance of carefully screening experimental drugs in appropriate preclinical models before embarking on the few clinical trials that are feasible in patients with these rare tumors cannot be overstated. Arakaki et al describe genetic and pharmacological screening approaches, including large-scale screening that is broad and encompassing but is costly and lengthy in time as well as smaller screens that are focused and biased. Small-scale pharmacology screening of FDA-approved and preclinical kinase inhibitors combined with computational machine learning algorithms is allowing the identification of downstream proteins and critical pathways that mediate tumor growth, which can be applied for these rare CNS cancers with known oncogenic drivers. Dr Taranjit S. Gujral Lab (Human Biology Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA) has used available data sets on kinase inhibitor profiles to select a small number of compounds to experimentally determine their effect on the growth and viability of cancer cells. The resulting data are then analyzed by machine learning models, leading to a ranked list of predicted kinases that can be validated with RNA interference (RNAi) approaches. The algorithm can predict response to drugs as a single agent or in combination. This computationally generated list of drugs can then be validated in genetically engineered mouse models. This powerful computational approach greatly streamlines the process of selecting drugs for further preclinical and clinical development that can be applied to other rare cancers.

In the second manuscript, Drew Pratt and colleagues describe state-of-the-art molecular testing for accurate classification of rare CNS tumors, which is an invaluable addition to traditional histopathology techniques. An accurate integrated diagnosis is a critical steppingstone that allows all subsequent care, including devising an effective management plan and estimating prognosis. Molecular testing can help confirm the diagnosis of tumor entities that can be otherwise difficult to properly classify, such as pleomorphic xanthoastrocytomas, which often share overlapping histopathology findings with glioblastomas but have a very different prognosis.[2] Additionally, molecular testing allows tumor subtyping (ie, medulloblastoma, ependymoma[3,4]) and inevitably leads to the description of new entities defined by their unique molecular features, such as, for example, MYCN-amplified ependymomas.[5,6] The authors highlight the risk of misdiagnosing rare tumors and stress the essential role of molecular analysis (including global DNA methylation and next-generation sequencing analysis) to reach an integrated diagnosis. The classification of CNS tumors is in fact a work in progress; many rare entities remain as "undiscovered islands,"[7,8] and there is a critical need for multi-institutional collaboration to further refine their classification in light of new molecular findings. Whereas these newly described tumor entities have molecular, clinical, and in retrospect, even histological features in common, they are so rare that a single neuropathologist or a local team would have never been able to identify a pattern leading to the description of a new tumor.

The third manuscript by Terri S. Armstrong and Mark. R. Gilbert describes how to take new discoveries into clinical trials to develop new treatments and improve care for people with rare CNS tumors. The biggest challenge in studying rare diseases in general, including rare CNS tumors, is patient accrual. With more in-depth study of these cancers, the challenge becomes even greater as distinct molecular subtypes with different prognoses and unique actionable molecular alterations are recognized. Further, limited funding is available to support these trials, and both patients and health care providers are often less informed of ongoing clinical trial opportunities. Several solutions are outlined, including expanding the eligibility of phase I studies in solid tumors and glioblastoma to include rare CNS tumors, adopting special trial designs such as umbrella, basket, and adaptive randomized studies, implementing pragmatic treatment plans such as the use of oral agents or infrequent administration, or alternatively, conducting research via a clinical trial network that reduces the travel and logistical issues for each patient. Whereas comparative randomized trials are often not feasible and historical comparisons can be inaccurate due to sparse and heterogenous retrospective data, the incorporation of standardized clinical outcome assessments (COAs), including patient-reported outcomes (PROs) in well-designed early-phase prospective studies may be sufficient to grant approval of new therapies when a clinical benefit can be clearly demonstrated. The FDA has defined clinical benefit as "a positive effect on how a person feels, functions, or survives."[9] Precedent for this in rare CNS tumors is already available. For example, the FDA approval of everolimus for the treatment of subependymal giant cell astrocytoma (SEGA)[10] based on objective response rate and improved quality of life, or the incorporation of temozolomide plus lapatinib[11] for treatment of recurrent ependymomas in adults in the National Comprehensive Cancer Network (NCCN) guidelines based on clear symptomatic improvement in patients with stabilization of disease.

Finally, we include here the link to a panel discussion with international neuro-oncology experts and leaders of projects and organizations (CERN, NCI-CONNECT, GLASS, International Low Grade Glioma Registry, and EURACAN) that have made significant progress to better understand rare CNS tumors and advance clinical care and research. This panel of experts discussed major real-world challenges, collaborative models that have successfully overcome some of them, and areas in critical need for further improvement (https://wfnos.org/panel-discussion-models-to-advance-science-and-outcomes-for-rare-cns-tumors/).

Deepening our understanding of these rare CNS tumors and implementing best care practices will ultimately improve patient outcomes and contribute to the setup of new models to improve care for people with all primary CNS tumors and also other cancers, which continue to be

reclassified in new molecularly defined and potentially actionable smaller subcategories (thus becoming "rare cancers"). Clearly, novel therapeutic approaches are needed and the path moving forward demands a few key elements: funding, bold ideas, trust, and increased multi-institutional and international collaboration.

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