JOURNAL OF CLINICAL ONCOLOGY SPECIAL SERIES OVERVIEW

Brain Tumors: Challenges and Opportunities to Cure

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Tumors of the CNS are among the most challenging malignancies to treat. Despite surgery, radiation, and chemotherapy, many patients have incurable cancers and suffer disabling symptoms. The median survival of patients with glioblastoma, the most common malignant adult brain tumor, remains less than 2 years, and brain tumors include the most common and difficult-to-treat malignancies in children. Although these statistics are daunting, recent advances in the understanding of brain tumor biology have fueled a new sense of optimism that more effective and less toxic treatments can be developed. This Special Series summarizes progress across a variety of adult and pediatric CNS malignancies with an eye toward future therapeutic opportunities. Some articles review current standard-of-care and practice-changing clinical trials among specific brain tumor types. Others summarize research findings that are shaping the way we think about brain tumors and that hold promise to advance novel treatments.

Whole-genome and RNA sequencing, as well as global epigenetic profiling, have revolutionized our understanding of pediatric brain tumors—they explain why these diseases, once regarded as histologically homogeneous cancers, display discrepant behaviors.[1-11] This new knowledge could improve the treatment of patients by pinpointing good-prognosis cohorts for reduced-treatment trials (which ultimately spares tissue from toxicity) and by targeting relatively poor-prognosis subtypes for novel treatment studies. In this regard, Mack and Northcott[12] provide an overview of approaches to supplement the current histopathologic classification of pediatric brain tumors with a variety of -omics approaches. Among malignant pediatric brain tumors, medulloblastoma is the most common and, arguably, the best understood. DNA and RNA microarray profiling techniques first demonstrated that these tumors comprise molecularly and clinically distinct tumor types, each marked by a unique transcriptional profile.[13-15] Subsequent cross-species genomic studies demonstrated that these transcriptional profiles likely echo those of the corresponding originating cell type in the developing hindbrain.[16] Armed with these and subsequent whole-genome sequencing data, Ramaswamy and Taylor[17] review changes in the classification, risk stratification, and treatment of medulloblastoma. Similar approaches have been used to better understand the cellular and molecular origins of ependymoma, the third most common type of pediatric brain tumor; however, treatment of this disease has been limited significantly by chemotherapy resistance.[18,19] Merchant[20] discusses the evolution of ependymoma therapy and, in particular, the efforts to reduce iatrogenic complications and increase disease control. Although less common than their adult counterparts, pediatric high-grade gliomas are among the most frequent and lethal childhood brain tumors. These highly heterogeneous tumors have provided some of the most intriguing sequencing results of any cancer to date, not least of which is the identification of recurrent somatic mutations in *H3F3A*, which encodes histone H3.3, or in the related *HIST1H3B*, which encodes histone H3.1.[8,9] These data have stimulated studies that provide insights into the basic biology of DNA metabolism and of brain tumor biology.[21,22] In another review, Sturm et al[23] discuss this complex set of pediatric brain tumors and explore new insights into tumor biology and clinical management. As well as being driven by sporadic somatic mutations, pediatric and adult brain tumors may arise in the context of germline tumor predisposition syndromes. Campian and Gutmann[24] review the spectrum and treatment of central nervous system tumors that arise in individuals with neurofibromatosis type 1 and neurofibromatosis type 2.

Gliomas represent the most common malignant brain tumors in adults and are highly heterogenous in their clinical presentation. Integrated genomic profiling has substantially advanced our understanding of this group of malignancies, including the identification of glioma core pathways in glioblastoma and isocitrate dehydrogenase mutations in low-grade gliomas.[25-27] These studies have provided a foundation for the additional classification of low-grade gliomas into distinct disease subgroups[28,29] and for an update of the WHO Classification of Tumors of the Central Nervous System.[30] Several articles in this series review this remarkable progress and its clinical implications. Diamandis and Aldape[31] summarize key insights from the molecular profiling of adult glioma and potential strategies for their clinical implementation. van den Bent et al[32] describe how the treatment of adult low-grade gliomas has evolved in recent years on the basis of results of recent clinical trials and reappraisal of prognostic disease biomarkers. Alexander and Cloughesy[33] review the current treatment of glioblastoma and highlight novel directions and opportunities for innovative clinical drug development. Two other articles in this series shed light on exciting progress in adult CNS tumors. Grommes and DeAngelis[34] provide an update on primary CNS lymphoma and strategies to incorporate molecularly targeted agents, such as inhibitors of deregulated B-cell receptor signaling, into the treatment of this disease. Barzilai et al[35] describe a state-of-the art multidisciplinary approach toward spinal metastasis, an increasingly common problem in adults with cancer.

Four final reviews address important concepts in the biology, diagnosis, and treatment of brain tumors that are applicable to

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both pediatric and adult cancers. The concept that cancers may be propagated by stem-like cells stretches back decades, and some of the first evidence that such cells exist in solid tumors was provided by studies of brain tumors.[36,37] Parada et al[38] review evidence for and against brain tumor stem cells and their implications for treatment. The intimate relationship of brain tumors to critical structures in the CNS renders imaging particularly important in disease management. Exciting advances in several new modalities are likely to provide real-time evaluation of the metabolism, treatment response, and microenvironment of brain tumors. Brindle et al[39] review existing and novel approaches to neuroimaging-based diagnosis, and Wen et al[40] review the use of imaging to evaluate brain tumor treatment. Finally, long-anticipated evidence that the immune system could be harnessed for therapeutic gain in the treatment of cancers has been provided by studies of various liquid and solid cancers.[41] Here, Sampson et al[42] provide insights into how immunotherapy might be developed for brain tumors.

All of the articles in this Special Series were graciously contributed by leaders in the field and highlight areas of substantial progress and extraordinary opportunity in neuro-oncology. However, we must learn from previous decades of failed drug development. Translation of new knowledge into effective therapies will require a much deeper understanding of actionable genetic alterations, of the contribution of drug targets to tumor maintenance, and of how best to integrate novel treatments with existing standard of care. Given the uncertainty of drug delivery across the blood-brain barrier and the lack of experimental models to reliably predict drug penetration in the CNS, the clinical evaluation of investigational agents also should include documentation of target inhibition in on-treatment biopsies and quantitative evaluation of drug-related effects on tumor growth rates, tumor metabolism, and tumor evolution. More extensive and comprehensive evaluation of cerebrospinal fluid for liquid biopsies may be informative in this regard.[43,44] And let us not forget to measure treatment effects that are perhaps less obvious to the oncologist but very real to the patient—for example, changes in seizure frequency, reductions in corticosteroid doses, avoidance of treatment-related cognitive changes. Although much work remains, the roadmap provided by recent biology and clinical advances provides us with the tools needed to generate real impact for patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

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DOI: https://doi.org/10.1200/JCO.2017.74.2965; published at jco.org on June 22, 2017.

Support

Supported by the National Brain Tumor Society, Grants No. 1R01NS080944-01 and P30-CA008748 from the National Institutes of Health, and Cycle for Survival (all to I.K.M.); and by funding from Cancer Research UK, Grants No. R01CA12951 and P01096832 from the National Cancer Institute, the RisingTide Foundation, CURESEARCH, and the Mathile Foundation (all to R.J.G.).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Ingo K. Mellinghoff
Consulting or Advisory Role: Agios

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No relationship to disclose