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Advances in brain tumors management: new perspectives and challenges

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Neuro-oncology is a rapidly evolving field, with significant advances recently made in our understanding of primary central nervous system (CNS) tumors biological mechanisms, the development of diagnostic and predictive biomarkers available in the clinics, and the identification of novel therapeutic strategies derived from basic and preclinical research. In the current issue of *Current Opinion in Neurology*, international experts provide an update on these issues, underlying their practical implications for neurologists.

Primary CNS tumors constitute a heterogeneous group of benign and malignant pathologies affecting children and adults. Over the past decades, advances in the understanding of CNS tumors biology have led to the identification of molecular alterations associated with specific phenotypes (clinico-radiological presentation, natural history). It was shown that these molecular alterations define distinct disease types and subtypes¹⁻⁶. For instance, within malignant diffuse gliomas commonly found in adults (adult-type, diffuse gliomas), it was recognized that the molecular status of mutations in the IDH genes (*IDH1* and *IDH2*) and co-deletion of the 1p and 19q chromosomal arms (1p/19q co-deletion) define three dominant types: oligodendrogliomas (IDH-mutant and 1p/19q codeleted), astrocytomas (IDH-mutant), and glioblastomas (IDH-wildtype). A key milestone was the demonstration that incorporating these molecular alterations in the diagnostic algorithm drastically improve diagnosis, resulting in groups that are more homogeneous, improved prediction of prognosis and treatment response. This major conceptual change led to incorporating molecular markers in the 2016 WHO classification of CNS tumors, whereas diagnosis before WHO 2016 was essentially based on histological features of tumors. In light of the rapid progress in biological insights, this trend intensified over the past years leading to several international conferences (cIMPACT-NOW) to evaluate novel findings and make recommendations on tumor classification⁷.

Jamshidi et al summarize the further advances made in the 2021 WHO classification of CNS tumors⁸⁻⁹, which provide substantial evidence for the growing role of molecular diagnostics in establishing a CNS tumor diagnosis. They summarize the major changes of the 2021 WHO classification, with a highlight on clinically pertinent updates. These changes include: i) updated criteria for tumor taxonomy, nomenclature and grading; ii) major updates in the classification of diffuse gliomas now being divided into three adult- and eight pediatric-types; iii) important changes in the classification of meningiomas and ependymomas; iv) recognition of

emerging entities associated with specific molecular drivers; and v) incorporation of methyloma as novel assay for the diagnosis of specific types. Among newly defined disease types, infant-type hemispheric gliomas constitute a novel group of high-grade glioma type occurring in newborns and infants characterized by the presence of specific molecular alterations (e.g. gene fusion involving ALK, ROS1, NTRK1/2/3, or MET). *Rosenberg et al* provide an overview of the molecular landscape of infant CNS tumors and therapeutic management of this population. The infants and young children is indeed characterized by a different landscape of tumor incidence (enrichment for rare types) as well as unique tumor biology. This population is also associated with unique challenges in terms of management due to potential toxicities of aggressive treatments to the developing brain. The authors provide an overview of the most common tumor types found in the infant population (medulloblastoma, atypical teratoid/rhabdoid tumors, embryonal tumors with multilayered rosettes, and choroid plexus tumors), discuss strategies for clinical diagnosis and tumor sequencing, and describe standard of care and precision oncology approaches based on molecular drivers and specific vulnerabilities in each tumor type. Primary central nervous system lymphoma (PCNSL) is another CNS tumor type that has recently seen advances on the molecular classification. *Hernández-Verdin et al* provide an overview of the recent developments in the field of molecular markers and targeted therapies in PCNSL. They summarize the key molecular alterations associated with lymphomagenesis and describe a novel multi-omics classification of PCNSL defining four different groups harboring different outcomes and clinical phenotypes. Interestingly the groups are associated with important differences in the composition of the tumor microenvironment composition (e.g. “immune hot”, “immune cold”), suggesting that tailored approaches such as immunotherapy could be used according to the different clusters. The authors also describe efforts for defining new therapeutic strategies in PCNSL, targeting the NF- κ B pathway or modulating the tumor microenvironment through immunomodulatory drugs or immunotherapy approaches.

These advances provide insights to better understand biology, manage patients, and conduct trials. They also highlight novel therapeutic strategies based on the identification and targeting of specific drivers or mechanisms associated with brain tumor development and progression. From a therapeutic standpoint, recent efforts have focused on two complementary strategies. On one hand, the targeting of

molecular drivers associated with CNS tumor development such as experimental therapeutic approaches targeting IDH mutations in diffuse gliomas. *de la Fuente* summarizes the tremendous progress achieved in this field over the past years. The review describes the ongoing areas of investigations (e.g. small-molecule inhibitors or vaccines targeting IDH mutant proteins, inhibition of pathways representing key vulnerabilities in gliomas with IDH mutations) and overviews the results of recent trials that tested these strategies, with a highlight on lessons learned from early clinical development and current challenges. Another area of intense investigation is the development of novel, efficient, immunotherapy strategies for brain tumors. In other cancer types (e.g. melanoma, lung cancer), the development of immunotherapy such as immune checkpoint blockade of the CTLA4 and PD1/L1 pathways has transformed the outcome of patients. Unfortunately, in CNS tumors, progress in this field has been limited. One key feature of CNS tumors potentially underlying this lack of efficacy is the presence of unique immune tumor microenvironment populations (e.g. microglia and other myeloid-derived cells) and strong enrichment with immunosuppressive pathways. *Richard et al* provide an overview of the recent advances in our understanding of gliomas tumor microenvironment and its role in driving immune evasion and more aggressive behavior. They highlight the recent advances made in the identification of immune cell subpopulations made thanks to novel technologies and describe key immunosuppressive features of gliomas including tumor-immune cell crosstalk associated with local and systemic immune dysfunction. In this line, *Andersen et al* describe the ongoing landscape of immunotherapy strategies tested in gliomas, including immune checkpoint blockade, antitumor vaccines, CAR-T cells, and oncolytic viruses. They overview the results of recent trials, including direct and indirect evidence from small populations suggesting that efficient antitumor immune responses can be reached within the CNS. They discuss the promises of further combinations of immunotherapy strategies to boost response, and the challenges associated with these complex trial designs (e.g. target/drug/population selection, treatment and dose combinations, safety). Among the critical challenges associated with immunotherapy strategies, *Cuzzubbo et al* review the recent advances in the field of neurological toxicities associated with immune checkpoint blockade. As indications for these treatments are growing and combinations – which are associated with higher risk of neurological toxicities – expanding, neurologists need to be aware of these rare but potentially life-

threatening adverse events in order to define optimal management along with oncologists. The review discusses the recent advances in understanding the pathophysiologic mechanisms of neurological toxicities associated with immune checkpoint blockade and potential implications for deciding rational treatments.

In all, admirable progress has been made over the past years. Translating these advances into improvements in the survival and quality of life of patients with brain tumors is the key challenge to achieve, especially for the tumor types still associated with poor outcomes. The recent developments and perspectives described in the current issue of *Current Opinion in Neurology* pave the way for reaching these key objectives.

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