Progress in treatment of gliomas

Patrick Y. Wen

Each year in the United States, there are over 80 000 patients diagnosed with primary brain tumors and approximately 26 000 of these are malignant [1]. Progress in treating these patients has been slow [2], but the past few years has seen important advances. The articles in this issue of *Current Opinion in Neurology* highlight some of this progress. These advances have been facilitated by the 2021 WHO Central Nervous System Tumor Classification, which incorporated molecular evaluation into tumor classification [3]. This classification distinguished adult-type from pediatric-type diffuse gliomas and separated isocitrate dehydrogenase (IDH) mutated oligodendrogliomas and astrocytomas from IDH-wildtype glioblastomas. This improved classification allows for better understanding of the prognosis and optimal therapy for patients and will enable more homogeneous populations of patients to be enrolled into clinical trials, facilitating the evaluation of novel therapies.

A major role of neurologists and neuro-oncologists looking after brain tumor patients is to provide them with the best supportive care to maximize their quality of life. The article by Ospina and Wen reviews the management of the major neurologic and medical complications in brain tumor patients. These include the optimal use of corticosteroids, antiseizure medications, strategies to improve fatigue and reduce cognitive impairment, and the increasing data suggesting direct oral anticoagulants are well tolerated for brain tumor patients in the management of venous thromboembolism.

Fuskushima and DeGroot (pp. 666–671) review the recent advances in therapies for glioblastoma. Glioblastomas are known to have a paucity of T cells and a suppressed immune environment, leading to repeated failures following treatment with immunotherapies, especially checkpoint inhibitors. They review current strategies under evaluation including vaccines, oncoviruses, CAR T-cell therapy and novel drug delivery techniques to overcome the challenges of the blood-brain barrier.

Song and Scott (pp. 672–681) review the advances in CAR T-cell therapy for gliomas. This treatment has transformed the management of hematologic malignancies. For gliomas, there have been encouraging responses in subsets of patients, especially those receiving GD2 CAR T-cells for H3K27 M mutated diffuse midline gliomas. They discuss the ongoing challenges of delivering CAR T-cells and sustaining responses, including the need for repeated intracranial administration. They also discuss emerging toxicities including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and tumor inflammation associated neurotoxicity syndrome (TIANS). As the use of CAR T-cell therapies for cancer patients increases, neurologists will encounter these complications with increasing frequency.

Epstein *et al.* (pp. 682–692) discuss the advances in focus ultrasound therapy. This is a growing treatment modality with multiple uses. When combined with intravascular microbubbles, it can transiently disrupt the blood-brain barrier and improve the delivery of novel therapies across the blood-brain barrier. It can also be used to enhance radiosensitization and immunotherapies. There is also growing interest in novel strategies using focused ultrasound for sonodynamic therapies and disrupting the blood-brain barrier to improve the yield for liquid biopsies.

Ruda *et al.* (pp. 693–701) summarize the current knowledge and future perspectives of liquid biopsy of blood and cerebrospinal fluid (CSF) for diagnosis and monitoring of primary CNS tumors. Liquid biopsies potentially can play a greater role in the management of CNS tumors compared to systemic tumors given the difficulties of performing repeated biopsies and surgeries in CNS tumors. Liquid biopsies may be useful for the diagnosis of brain tumors, avoiding biopsies, detecting of minimal residual disease after surgery, determining early response or progression after radiotherapy, chemotherapy or targeted agents, and outcome prediction. Potential analytes include circulating tumor cells,

Center For Neuro-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

Correspondence to Patrick Y. Wen, MD, Center For Neuro-Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA.
E-mail: patrick_wen@dfci.harvard.edu

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circulating cell-free tumor DNA, circulating cell-free RNA, circulating proteins and metabolites, extracellular vesicles and tumor-educated platelets. However, the blood-brain barrier currently limits the ability to detect these in the blood leading to increasing interest in liquid biopsies in the CSF.

Perhaps the area where there has been the greatest progress is in the treatment of low-grade gliomas. These tumors have traditionally been treated with surgery, radiotherapy and chemotherapy with significant long-term toxicities. Demaliaj and Gardner (pp. 702–707) review the advances in the treatment of pediatric low-grade gliomas. The improved understanding of the molecular drivers of these tumors, especially mitogen-activated protein kinase (MAPK) alterations either with BRAF V600E point mutations or BRAF fusions, has led to the development of targeted therapies for these patients. Dabrafenib (RAF inhibitor) and trametinib (MEK inhibitor) were approved by the Food and Drug administration for pediatric low-grade gliomas in 2023 [4], and the type 2 RAF inhibitor tovarafenib was approved for pediatric low-grade gliomas with BRAF alterations in 2024 [5]. These important advances increase the treatment options for these patients, although their long-term side effects will need to be determined.

Baek *et al*. (pp. 708–716) review the recent advances in therapies for IDH-mutated low-grade gliomas in adults. Because IDH mutations are defining molecular drivers of WHO grade 2–4 astrocytomas and oligodendrogliomas, there has been significant interest over the past decade in developing IDH inhibitors to treat these tumors. A series of studies, culminating in the INDIGO trial, demonstrated that the brain penetrant IDH I/2 inhibitor vorasidenib significantly prolonged progression-free survival and time-to-next tumor intervention in grade 2 IDH-mutated gliomas who have only had surgery [6]. This represents the first new treatment for low-grade gliomas since the introduction of temozolomide in 1999 and will significantly change the management of these patients. The increased understanding of the biology of these tumors has also led to studies evaluating other therapeutic approaches such as immunotherapies and other targeted therapies.

In a field where progress has been unacceptably slow, there have been important advances recently, especially for the treatment of lower grade gliomas. These advances will have a significant beneficial impact on the management of these patients.

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Conflicts of interest

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