NCCN Guidelines for Central Nervous System Cancers: Updates in the Treatment of Adult Patients With Glioma

Presented by Craig M. Horbinski, MD, PhD, and L. Burt Nabors, MD

ABSTRACT

In 2021, the WHO revised its classification of central nervous system (CNS) tumors, which has resulted in changes to both the diagnostic and treatment landscapes. At the NCCN 2023 Annual Conference, this tumor board-style presentation featured 4 case studies to demonstrate an evidence-based approach to the treatment of patients with various WHO-defined types of diffuse glioma. The NCCN Guidelines have been updated to reflect the WHO reclassification of CNS tumors and provide treatment recommendations accordingly.

“Using the reclassification of gliomas by the WHO criteria, we can resolve a lot of cases that otherwise were a bit of a coin toss,” commented Craig M. Horbinski, MD, PhD, Professor of Pathology and Neurological Surgery, Director of Neuropathology, Northwestern University and Northwestern Memorial Hospital, and member of the NCCN Guidelines Panel for Central Nervous System (CNS) Cancers. At the NCCN 2023 Annual Conference, together with L. Burt Nabors, MD, Vice Chair for Research of Neurology and Neurosurgery, Professor and Director, Division of Neuro-Oncology, University of Alabama at Birmingham O’Neal Comprehensive Cancer Center, and Chair of the NCCN Guidelines Panel for CNS Cancers, used 4 case studies, clinical trial data, and the updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CNS Cancers to illustrate an evidence-based approach to the treatment of patients with the current WHO-defined types of adult-type diffuse glioma.

Published in 2021, the 5th edition of the WHO classification of CNS tumors regrouped diffuse gliomas into 2 primary categories: adult-type and pediatric-type. Adult-type CNS tumors, which was the focus of the presentation, comprises IDH-mutant astrocytomas, IDH-mutant oligodendrogliomas with 1p/19q codeletion, and IDH–wild-type glioblastomas.

Case 1: WHO Grade 4 IDH–Wild-Type Glioblastoma

The first case focused on a 64-year-old male with a 2-week history of slurred speech and worsening incidences of headaches and falling. Imaging studies revealed a right temporal mass and edema. He subsequently underwent a near-complete surgical resection and achieved some degree of edema reduction. Upon histopathologic examination, Dr. Horbinski observed hypercellularity and some scattered mitoses. There did not appear to be any necrosis or microvascular proliferation; however, intravascular thrombosis was present.

“This raises a strong possibility that this is going to be an IDH–wild-type glioblastoma,” he remarked. “When next-generation sequencing was performed, we proved that it was wild-type for both IDH1 and IDH2, had TERT promoter mutation, EGFR amplification, gain of chromosome 7, and loss of chromosome 10.” The tumor was also found to be immunonegative for the canonical IDH1 R132H mutation.

To aid in the evaluation of the present case, Dr. Horbinski introduced an adult-type diffuse glioma decision tree (Figure 1). The updated WHO classification criteria and aforementioned clinical and neuropathologic characteristics ultimately pointed to a diagnosis of WHO grade 4 IDH–wild-type glioblastoma. “One of the biggest advances now for these tumors [is that] you do not necessarily need to have all of the histopathologic criteria to call something a glioblastoma anymore,” commented Dr. Horbinski.

“[A tumor is tantamount to a glioblastoma by the current WHO scheme] as long as you can prove it is an [IDH]–wild-type tumor and has ≥1 of the following: EGFR amplification, gain of chromosome 7 and loss of chromosome 10, and TERT promoter mutation.”
Per the NCCN Guidelines, standard radiation therapy (RT) + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy is preferred for patients with glioblastoma who are aged <70 years, have a good performance status, and have either a methylated or indeterminate MGMT promoter status. However, of note, clinical trial enrollment remains the top treatment recommendation, according to Dr. Horbinski.

Dr. Nabors noted that most of the evidence supporting this preferred regimen classification came from a study published in 2005, in which the median durations of overall survival (OS) and progression-free survival appeared to be prolonged with the addition of concomitant or adjuvant temozolomide to RT. An accompanying paper demonstrated that, if the MGMT gene promoter is active, the glioblastoma is rendered resistant to treatment with temozolomide. Patients with a positive methylation status seemed to experience significantly improved OS outcomes compared with their counterparts with a nonmethylated status.

As a closing caveat, Dr. Nabors discussed response assessment in relation to pseudoprogression after RT. “Typically, the first MRI, which is often 1-month post-treatment, may actually look worse; there may be increased enhancement and edema,” he explained. “You need to prewarn [patients] that the criteria for [disease] progression at 1 month [after RT] is disease change outside of the field of radiation.”

Case 2: WHO Grade 4 IDH-Mutant Astrocytoma
The second case presentation focused on a 29-year-old male who underwent surgical resection for an enhancing mass in the left frontal lobe. Unlike the previously described case, histopathologic examination revealed both necrosis and microvascular proliferation.

“[The lack of intratumoral microthrombi] strongly suggests this may be an IDH-mutant tumor because, for a number of reasons, [these] tumors suppress thrombosis,” Dr. Horbinski commented. “Which is what was observed by immunostaining the canonical IDH1 R132H variant.” Next-generation sequencing confirmed the presence of this mutation, as well as mutations in ATRX and TP53, and homozygous deletion of CDKN2A/B.

Based on the adult-type diffuse glioma decision tree (Figure 1), the patient presented with sufficient neuropathologic features to be diagnosed with a WHO grade 4 IDH-mutant astrocytoma. Dr. Horbinski noted this would likely have been classified as a glioblastoma just a few years ago. “These IDH-mutant tumors have fundamentally different genomics, tumor metabolism, disease course, and response to therapy,” he explained. “[We] try to distinguish them from glioblastomas as much as possible and reserve ‘glioblastoma’ just for those that are IDH–wild-type and has those other criteria that was discussed earlier.”

Prior to the WHO reclassification of CNS tumors, clinical trials designed for patients with glioblastoma often enrolled those with WHO grade 4 IDH-mutated astrocytoma. “When you look at median OS for a glioblastoma, the numbers we quote are really actually inflated because they are from trials that had these [patients with] IDH-mutated disease in them,” Dr. Nabors commented. Dr. Horbinski added that “not all of the studies on this subject incorporated molecular data.”
According to Dr. Nabors, molecular diagnostics are of critical importance prior to clinical trial enrollment. Currently, there are limited clinical trials enrolling patients with WHO grade 4 IDH-mutated astrocytoma. However, there is an ongoing effort to expand the number of studies allowing for the inclusion of this population.

**Case 3: WHO Grade 2 IDH-Mutated Astrocytoma**

The third case presentation featured a 31-year-old male with a remote history of concussion who, approximately a decade later, experienced a new-onset partial seizure. On imaging, an abnormality was detected at the time of concussion, which gradually developed a growth with mass effect and edema; it was ultimately completely surgically resected. Histologic examination revealed no necrosis, microvascular proliferation, or mitotic activity. The resected specimen demonstrated mutations in *IDHI* R132C, ATRX, and TP53, as well as gain of chromosome 7.

“When you see [mutation of *IDHI*] R132C, that is nearly always the purview of astrocytomas,” Dr. Horbinski remarked. “In other words, oligodendrogliomas [almost] never have [mutation of *IDHI*] R132C, for reasons we do not know.”

Based on the adult-type diffuse glioma decision tree (Figure 1), a diagnosis of IDH-mutated astrocytoma could be made. However, in this case, the presence of less-aggressive histopathologic features established it as WHO grade 2. “This is a classification change; you may have historical patients with a diagnosis called a ‘mixed glioma’ or an ‘oligoastrocytoma,’ [but] that term is really no longer used,” Dr. Nabors explained. “Now we are very clear: you either have an astrocytoma or an oligodendroglioma.”

In general, WHO grade 2 and 3 IDH-mutant gliomas are more commonly diagnosed in relatively younger adults. Seizures are frequently reported in this patient population and, according to Dr. Nabors, they should be treated with an anticonvulsant. This population is, overall, a heterogeneous group with varying clinical behavior. However, known prognostic factors may aid in the prediction of outcomes.

“Two studies are driving our recommendations for grade 2 and 3 astrocytomas right now,” Dr. Nabors remarked. Based on the results of the phase III RTOG 9802 trial, the administration of chemotherapy with procarbazine + lomustine and vincristine after RT appeared to improve both progression-free survival and OS outcomes in patients with high-risk, low-grade glioma. In the phase III CATNON trial, patients with WHO grade 3 IDH-mutated...
astrocytoma who underwent RT were found to derive an OS benefit from adjuvant treatment with temozolomide; this did not seem to hold true with concurrent administration.5

The results of these trials are reflected in the NCCN Guidelines (Figure 2).1 RT plus adjuvant chemotherapy with procarbazine/lomustine/vincristine is recommended for patients with high-risk WHO grade 2 IDH-mutated astrocytoma, whereas RT plus 12 months of adjuvant temozolomide is the preferred regimen for those with WHO grade 3 IDH-mutated astrocytoma.

Surgical resection has also been found to be of critical importance in the treatment of IDH-mutated astrocytoma. According to Dr. Nabors, several studies have demonstrated a link between the extent of surgical resection of the FLAIR abnormality and improved outcomes.

Case 4: WHO Grade 3 IDH-Mutated Oligodendroglioma

The fourth and final case presentation focused on a 64-year-old female with new-onset seizures who underwent partial resection of the right temporal lobe. Histologically, the resected specimen demonstrated irregular nuclei and elevated mitoses. Molecular analyses revealed the presence of both canonical IDH1 R132H and TERT promoter mutations, as well as 1p/19q codeletion.

"In this case, the tumor has retained ATRX expression, which suggests it does not have an ATRX mutation [and] is probably an oligodendroglioma," Dr. Horbinski commented. "Oligodendrogliomas tend to have TERT promoter mutations, not ATRX mutations."

Based on the adult-type diffuse glioma decision tree (Figure 1), the resected specimen had neuropathologic characteristics to warrant a diagnosis of IDH-mutated oligodendroglioma. The elevated presence of mitoses solidified it as WHO grade 3 versus grade 2.

According to the NCCN Guidelines (Figure 2), consideration of a clinical trial is the preferred treatment approach for eligible patients with WHO grade 3 IDH-mutated oligodendroglioma.1 There is category 1 evidence supporting the efficacy of RT in combination with neoadjuvant or adjuvant chemotherapy with procarbazine + lomustine and vincristine in this setting; according to Dr. Nabors, the foundation for this recommendation was provided by the RTOG 94-02 and EORTC 26951 trials. Furthermore, the guidelines allow for the use of temozolomide in the adjuvant or both adjuvant and concurrent settings.

"[In] this population with WHO grade 3 oligodendroglioma, RT and chemotherapy are better than RT alone," Dr. Nabors remarked. "The existing data support first-line treatment with both." The phase III CODEL study, which will evaluate RT in combination with either adjuvant procarbazine + lomustine and vincristine versus concomitant and adjuvant temozolomide, should shed light on the optimal chemoradiotherapy approach in this clinical context.

Disclosures: Dr. Horbinski has disclosed no relevant financial relationships. Dr. Nabors has disclosed serving as a scientific advisor for Chimerix.

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References