Editorial

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A new era after a long wait: Vorasetinib, an inhibitor of mutant IDH1 and IDH2 enzymes in patients with IDH-mutant glioma

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Patients with cerebral neoplasms have waited many years for effective molecularly-targeted treatment.

In the September issue of the *New England Journal of Medicine*, Mellinghoff IK et al. reported the results of the INDIGO trial, opening new horizons.[1]

This study involved Vorasetinib, an oral brain-penetrant inhibitor of mutant IDH1 and IDH2 enzymes, in patients with isocitrate dehydrogenase (IDH)-mutated glioma. IDH is an enzyme that catalyses the oxidative decarboxylation of isocitrate and therefore plays a key role in the Krebs cycle.

A heterozygous point mutation in IDH1 causing an arginine to histidine substitution at amino acid 132 (IDH1 R132H) is found in most IDH-mutant gliomas.[2] This gain-of-function mutation disrupts the conversion of isocitrate to alpha-ketoglutarate (α-KG) and instead favours the production of large amounts of the 'oncometabolite' D-2-hydroxyglutarate (D-2HG).

The most common primary adult brain tumor diagnosed in patients under 50 is isocitrate dehydrogenase (IDH)-mutant glioma.

In the Cancer Registry of the United States (CBTRUS) dataset, for cases diagnosed in 2018, the overall age-adjusted incidence of IDH-mutant gliomas in the US was 0.70/100,000 persons.[3] IDH-mutant tumors accounted for approximately 12% of all gliomas diagnosed, with a very high frequency in IDH-mutant and codeleted 1p and 19q oligodendrogliomas, where it occurs in almost as much as 90% of cases regardless of grading, and in non-co-deleted IDH-mutant astrocytomas, where it affects approximately 35% of patients. Grade 4 glioblastomas and astrocytomas expressing the IDh mutation are a numerically tiny group.

The INDIGO trial (NCT04164901) is a randomized, double-blind, controlled phase III trial. A total of 340 patients with mutant grade II gliomas were enrolled, including oligodendrogliomas and astrocytomas, and randomized (1:1) to receive vorasetinib or placebo. Patients were eligible if they were 12 years or older and had histologically confirmed grade 2 residual or recurrent oligodendroglioma or astrocytoma (according to WHO 2016 criteria) with centrally confirmed IDH1 and IDH2 mutation status. Other critical eligibility criteria included a Karnofsky performance status (KPS) score of at least 80, at least one previous surgery (with the most recent surgery occurring between one and five years before randomization), no other anticancer treatment for glioma, and no use of steroids for signs or symptoms of glioma.

Of note, patients should be considered by investigators to be appropriate candidates for a watch-and-wait approach and not to be at high risk (with uncontrolled seizures, brainstem involvement, and clinically relevant functional or neurocognitive deficits caused by the tumor).

Patients had measurable, non-enhancing disease assessed centrally and these were patients with non-enhancing neoplasms who had undergone surgery. They had not received any postoperative treatment (radiotherapy or chemotherapy), and after a median of three years from histological diagnosis, they were included in the trial.

One hundred sixty-seven patients received active treatment with vorasetinib at 40 mg QD orally for 28 days until disease progression. The patients in the control group (170) received a placebo. Patients with radiographic evidence of progressive disease could cross from placebo to active treatment.

The primary endpoint of the study was progression-free survival (PFS). PFS was defined as the time from randomization to first disease progression (PD) according to RANO-LGG criteria or death from any cause. A key secondary endpoint was the time from randomization to the next intervention, defined as the initiation of anticancer

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treatment necessitated by disease progression or death from any cause.

After a median follow-up of 14.2 months (a follow-up that, given the characteristics of the patients, could be considered relatively short), 226 patients (68.3%) were still receiving vorasetinib or placebo. The primary endpoint, PFS, was significantly better with vorasetinib than with placebo (median PFS: 27.7 months versus 11.1 months; hazard ratio for progression or death, 0.39; 95% confidence interval [CI] 0.27 to 0.56; $P < 0.001$). Time to next intervention was significantly better in the vorasetinib group than in the placebo group (hazard ratio, 0.26; 95% CI, 0.15 to 0.43; $P<0.001$). Grade 3 or higher adverse events occurred in 22.8% of patients receiving vorasetinib and 13.5% receiving placebo. The most common toxicity was a grade 3 or higher increase in alanine aminotransferase, which occurred in 9.6% of patients receiving vorasetinib.

The study is a demonstration of the efficacy and tolerability of vorasetinib in the treatment of patients with untreated IDH-mutant low-grade gliomas. It represents a potentially practice-changing trial, since vorasetinib was shown to be able to delay more aggressive treatments, such as radiotherapy and chemotherapy, that may be associated with short- and long-term toxicities in a patient population that tends to be younger.[4,5] However, a certain degree of caution should be applied due to the number of patients treated and the limited follow-up period and moreover, this trial generated some food for thought.

From a biological point of view, enhancing IDH-mutant tumors failed to respond to vorasetinib in previous nonrandomized studies, suggesting that the presence of enhancement could be an expression of changes in the molecular profile that impair vorasetinib activity. This provided a rationale for the early use of this drug before radiotherapy and chemotherapy.[6]

One point that will be crucial for future management of patients with IDH-mutant low-grade gliomas is patient selection: in fact, it is not fully clear which patients can safely wait for at least one year after surgery before receiving active treatment.[7] Further efforts should be made to identify these "intermediate" risk patients in the future.

vorasetinib could become a new standard of care for patients with low-grade IDH1/2-mutant gliomas. However, one of the critical issues is the timing of treatment initiation in patients who have had surgery. To date, we have no definite criteria for defining when therapy should start. Indeed, there are no molecular indicators that can help us in this choice. One criterion that could be used is the lesion size before surgery. A large tumor, even if it has been extensively resected, requires a more aggressive approach.

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