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INDIGO: Example of inappropriate crossover and why PFS cannot be the primary outcome in gliomas

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Introduction

Vorasidenib has been praised as a medical advance for patients with low-grade glioma, a disease with little drug development in over two decades. Patients who have low-grade glioma, but are considered to have high-risk disease, are eligible for further treatment. Nevertheless, it is accepted practice to delay radiotherapy, based on randomized data that showed no difference in overall survival (OS) between those who received early versus late radiotherapy [1]. Moreover, radiotherapy is presumed to possibly cause long-term toxicities, including neurocognitive dysfunction [2], and its effects on quality of life (QoL) and cognitive function are unknown.

The INDIGO study included 331 adult patients with residual or recurrent IDH-mutant grade 2 gliomas who had received no previous systemic treatment and were within 1–5 years from latest surgery [3]. Patients receiving vorasidenib demonstrated a significant reduction in tumor progression or death compared to patients receiving placebo (HR = 0.39; 95% CI, 0.27–0.56), with a median of 27.7 months versus 11.1 months. As a secondary outcome, the likelihood of being alive and not receiving further treatment at 18 months was 85.6% in the vorasidenib group and 47.4% in the placebo group. While these results appear impressive, there are at least 3 concerns about the study design that may limit their interpretability: 1) inappropriate use of crossover in the control arm, 2) questionable use of a surrogate endpoint, and 3) lack of QoL assessment.

Section snippets

Crossover

Crossover is necessary in randomized trials when a drug is already an approved subsequent standard of care and a trial tests routine upfront use, but it can confound study interpretation if a drug is being tested for the first time in a disease setting [4]. In the INDIGO trial, control arm patients who had tumor progression were given access to the novel agent. This resulted in vorasidenib being administered to 90% of patients receiving subsequent therapy in the control arm.

The use of crossover …

Progression events

It is noteworthy that among 88 progression events in the placebo group, 58 (65%) received a subsequent line of treatment, while 19 out of 47 (40%) patients progressing on the experimental arm received a subsequent line. This supports the hypothesis that many patients were still deemed eligible for a watch and wait approach upon progression. The use of progression-free survival (PFS) as an outcome is not justified in this setting. Prior first-line studies introducing the use of the combination…

Cost and toxicity

With a median PFS of 27 months in the experimental group, over half of the patients remained on vorasidenib for at least 2 years. In this case, it is essential to consider cost and toxicity, especially since these tumors often affect young people with long survival, often resulting in a need to balance treatment with QoL. The article reports few adverse events except for low grade hepatotoxicity (9.6% were grade 3). Also, there was no difference in seizure occurrence between the two arms,…

Response assessment and intermediate endpoints in gliomas

PFS was defined as the time between randomization and the first documented progression on imaging by blinded and independent evaluation, according to the Response Assessment for Neuro-oncology for Low-Grade Gliomas (RANO-LGG) criteria, or death. The RANO-LGG criteria, as a modified version of RANO, introduced the concept of minor response and it also reiterates that any new contrast enhancement on scans constitutes disease progression [9]. However, the expected new RANO 2.0 criteria do not…

Taking a drug to avoid taking a drug

A goal of the INDIGO trial was to delay time until further treatment, yet this obfuscates the fact that patients in the intervention arm were required to take a treatment to do so. Testing an active intervention against a placebo-controlled arm (i.e., no treatment) is incongruous with the goal of reducing treatment. Vorasidenib is a treatment, and the research questions regarding its testing should reflect this. Assuming long-term vorasidenib therapy is more acceptable to patients than other…

Conclusion

In conclusion, there is great interest in advances in glioma treatment. However, vorasidenib's positive findings were based on a primary outcome of negligible value to patients. Patients want to live longer, and if not, at

least live better. Based on the INDIGO study, it is impossible to say whether vorasidenib can provide either. It offers significant cost and some toxicity, but there is no clear evidence that it is superior to prevailing standard of care.…

Disclosure

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Miguel Zugman: Writing – original draft, Conceptualization. **Vinay Prasad:** Writing – review & editing, Supervision. **Alyson Haslam:** Writing – review & editing.…

Declaration of Competing Interest

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