Title

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

Authors

Zugman, Miguel
Haslam, Alyson
Prasad, Vinay

Publication Date

2024-06-01

DOI

10.1016/j.jcpo.2024.100476

Peer reviewed

Journal of Cancer Policy 40 (2024) 100476

Contents lists available at ScienceDirect

Journal of Cancer Policy

journal homepage: www.elsevier.com/locate/jcpo

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

1. 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.

2. 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 in INDIGO was problematic. First, it is unclear if vorasidenib is the best therapy upon progression, and crossover may delay access to life prolonging therapies. Second, a high rate of crossover limits interpretation of OS. If survival is increased, it could be due to early use of vorasidenib in the experimental arm, but an alternate explanation is that it delayed access to life prolonging therapy in the control group [5]. If the survival is the same, it could be due to the crossover to an effective therapy, thus the subsequent treatment "diluted" the early benefit derived from early use of vorasidenib. Alternatively, it could be that the drug has no effect on survival, or off-target harms negate benefit. Statistical methods like rank preserving structural failure time models may attempt to correct for this, but this involves the core assumption that the drug works [6].

The authors provide no justification for permitting crossover. The proposed goal of the intervention was to postpone the initiation of radiotherapy with chemotherapy, deemed as eventually indispensable. Patients included in the trial were already considered eligible for chemoradiation treatment upon recruitment, so how could participants in the control arm who showed signs of disease progression still be candidates for a therapy which sole purpose was to delay definitive treatment? A viable explanation is that the investigators were not worried about promptly initiating radiotherapy unless patients showed other signs of high-risk disease, such as clinical symptoms or new enhancement on imaging, although this is not completely clear.

3. 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 of procarbazine, lomustine, and vincristine in this disease had OS as the primary outcome [7].

Additionally, the authors assume that delaying definitive treatment would improve outcomes as standard treatments can induce tumor transformation to hyper-mutational states linked to therapy resistance and rapid progression. On the other hand, it is unknown which tumoral changes could be triggered by the use of IDH inhibitors and how the disease would behave after progression on these treatments. IDH inhibitor's presumed mechanism of action should induce tumor differentiation, but pre-clinical models also showed that loss of heterozygosity of the IDH-mutant gene was associated with aggressive phenotypes. The role of IDH mutations seems also to be histology dependent and dynamic according to timing of tumorigenesis [8]. In this way, the INDIGO trial would provide useful information if comprehensive molecular tumor assessments were performed in patients that were both exposed to vorasidenib and later received salvage surgery. Until such analyses are done, PFS will remain an unreliable surrogate endpoint, as no previous study has shown its validity in this setting.

4. 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,

https://doi.org/10.1016/j.jcpo.2024.100476
Received 17 January 2024; Received in revised form 27 March 2024; Accepted 5 April 2024
Available online 6 April 2024

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, although the anticipated peer-reviewed report on QoL and seizure frequency has yet to be published. For patients who are continuously kept on treatment, QoL assessments are indispensable. While current standard treatments for low-grade gliomas have fixed durations in which transient deterioration of QoL are expected, continuous treatment until disease progression or limiting toxicity can only be justified by better symptom control (such as reduced seizures) or long-term health-related QoL benefits, which are yet to be presented as secondary endpoints. However, patients in the placebo group who progressed also became candidates for the drug. Only 6 patients (10%) of the placebo group who received a subsequent line of therapy were given a treatment that was not vorasidenib (e.g., crossover). It is unclear which exact treatments they were, as it could have been radiotherapy or even salvage surgery. Nonetheless, it is difficult to claim that an intervention delays the introduction of radiotherapy when such a small percentage of patients in the study actually received this treatment.

5. 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 further differentiate between high-grade and low-grade lesions, as that cannot be defined only by lesion enhancement. While increasing attention has been given to new ways of assessing tumor response, including tumor growth rate, volumetric assessment, and advanced imaging techniques, RANO 2.0 will keep two-dimensional evaluations as the primary form of measurement [10]. However, two-dimensional measurements are limited by poor-to-moderate inter-operator reproducibility [11]. Although development of intermediate endpoints for the study of novel therapeutics in glioma is desirable in order to accelerate the availability of new drugs, the limitations and shortcomings of such endpoints cannot be overemphasized. A more promising alternative would be to incorporate clinical outcome assessments along with imaging criteria in future clinical trials [12].

6. 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 treatments upon progression (which remains unproven), future trials may focus on whether treatment with vorasidenib delays time until aggressive and established treatment, not any subsequent therapy. Ideally, longitudinal health-related QoL will help to adjudicate if the benefits of the delayed treatment outweigh the harms of treatment [13].

7. 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

V.P. receives research funding from Arnold Ventures through a grant made to UCSF, and royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts, and runs a YouTube channel, which collectively earn revenue on the platforms: Patreon, YouTube and Substack. MZ and AH have no disclosures to report.

Funding

Arnold Ventures.

CRediT authorship contribution statement

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

Declaration of Competing Interest

Disclosure: V.P. receives research funding from Arnold Ventures through a grant made to UCSF, and royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts, and runs a YouTube channel, which collectively earn revenue on the platforms: Patreon, YouTube and Substack. MZ and AH have no disclosures to report.

References

[1] M.J. van den Bent, D. Afra, O. de Witte, et al., Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial, Lancet 366 (9490) (2016) 985–990, https://doi.org/10.1016/S0140-6736(05)67070-5.

[2] S. Tabrizi, B.Y. Yeap, J.C. Sherman, et al., Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma, Radiother. Oncol. 137 (2019) 95–101, https://doi.org/10.1016/j.radonc.2019.04.027 (Mellinghoff IK, van den).

[3] M.J. Bent, D.T. Blumenthal, et al., Vorasidenib in IDH1- or IDH2-mutant low-grade glioma, N. Engl. J. Med. (2023), https://doi.org/10.1056/nejmoa2304194 (Published online August 17).

[4] A. Haslam, V. Prasad, When is crossover desirable in cancer drug trials and when is it problematic? Ann. Oncol. 29 (5) (2018) 1080, https://doi.org/10.1093/annonc/mdy116.

[5] T. Olivier, A. Haslam, V. Prasad, Post-progression treatment in cancer randomized trials: a cross-sectional study of trials leading to FDA approval and published trials between 2018 and 2020, BMC Cancer 23 (1) (2023), https://doi.org/10.1186/s12885-023-10917-z.

[6] V. Prasad, M.S. Kim, A. Haslam, Cross-sectional analysis characterizing the use of rank preserving structural failure time in oncology studies: changes to hazard ratio and frequency of inappropriate use, Trials 24 (1) (2023), https://doi.org/10.1186/s13063-023-07412-y.

[7] A.B. Lassman, K. Hoang-Xuan, Mei-Yin, et al., Joint Final Report of EORTC 26951 and RTOG 9402: Phase III Trials With Procarbazine, Lomustine, and Vincristine Chemotherapy for Anaplastic Oligodendroglial Tumors, vol 40, 2022. (https://doi.org/10).

[8] C.J. Pirozzi, H. Yan, The implications of IDH mutations for cancer development and therapy, Nat. Rev. Clin. Oncol. 18 (10) (2021) 645–661, https://doi.org/10.1038/s41571-021-00521-0 (Epub 2021 Jun 15. PMID: 34131315).

[9] U.N. Chukwueke, P.Y. Wen, Use of the Response Assessment in Neuro-Oncology (RANO) criteria in clinical trials and clinical practice, CNS Oncol. 8 (1) (2019)

CNS28, https://doi.org/10.2217/cns-2018-0007 (Epub 2019 Feb 26. PMID: 30806082; PMCID: PMC6499019).
[10] P.Y. Wen, M. van den Bent, G. Youssef, T.F. Cloughesy, B.M. Ellingson, M. Weller, E. Galanis, D.P. Barboriak, J. de Groot, M.R. Gilbert, R. Huang, A.B. Lassman, M. Mehta, A.M. Molinaro, M. Preusser, R. Rahman, L.K. Shankar, R. Stupp, J. E. Villanueva-Meyer, W. Wick, D.R. Macdonald, D.A. Reardon, M.A. Vogelbaum, S. M. Chang, RANO 2.0: update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults, J. Clin. Oncol. 41 (33) (2023) 5187–5199, https://doi.org/10.1200/JCO.23.01059 (Epub 2023 Sep 29. PMID: 37774317; PMCID: PMC10860967).
[11] F. Raman, A. Mullen, M. Byrd, S. Bae, J. Kim, H. Sotoudeh, F.E. Morón, H. M. Fathallah-Shaykh, Evaluation of RANO criteria for the assessment of tumor progression for lower-grade gliomas, Cancers 15 (13) (2023) 3274, https://doi.org/10.3390/cancers15133274 (PMID: 37444384; PMCID: PMC10340202).
[12] E. Vera, A. Christ, E. Grajkowska, N. Briceno, A. Choi, S.K. Crandon, K. Wall, M. Lindsley, H.E. Leeper, J. Levine, J. Reyes, A.A. Acquaye, A.L. King, V. Jammula, K. Roche, J.L. Rogers, M. Timmer, L. Boris, N. Lollo, M. Panzer, L. Polskin, T. Pillai, E. Burton, M. Penas-Prado, B. Theeler, M.R. Gilbert, T.S. Armstrong, T.R. Mendoza, Relationship between RANO-PRO Working Group standardised priority constructs and disease progression among malignant glioma patients: a retrospective cohort study, EClinicalMedicine 55 (2022) 101718, https://doi.org/10.1016/j.eclinm.2022.101718 (PMID: 36386035; PMCID: PMC9661442).
[13] A. Haslam, D. Herrera-Perez, J. Gill, V. Prasad, Patient experience captured by quality-of-life measurement in oncology clinical trials, JAMA Netw. Open 3 (3) (2020) e200363, https://doi.org/10.1001/jamanetworkopen.2020.0363 (PMID: 32129865; PMCID: PMC7057133).

Miguel Zugman[a], Alyson Haslam[a,b], Vinay Prasad[b,*]
[a] *Centro de Oncologia e Hematologia Einstein Família Dayan-Daycoval, Hospital Israelita Albert Einstein, São Paulo, Brazil*
[b] *University of California San Francisco, 550 16th St, 2nd Fl, San Francisco, CA 94158, United States*

[*] Correspondence to: Department of Epidemiology and Biostatistics, UCSF Mission Bay Campus | Mission Hall: Global Health & Clinical Sciences Building | 550 16th St, 2nd Fl, San Francisco, CA 94158, United States.
E-mail address: Vinayak.prasad@ucsf.edu (V. Prasad).