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EDITORIAL

Molecular imaging of IDH-mutant gliomas in the new era of IDH inhibitors: preparing for future challenges

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June 2023, with the presentation of the results of the phase 3 INDIGO trial at the 2023 ASCO Annual Meeting II, marked a new era for patients with isocitrate dehydrogenase (IDH) mutant gliomas: vorasidenib, a second-generation oral inhibitor of mutant IDH1/2 enzymes, significantly improved median progression-free survival and delayed the initiation of chemoradiotherapy in patients with residual or recurrent grade 2 IDH-mutant gliomas.

Proven efficacy and safety currently make vorasidenib the ideal candidate for treating grade 2 IDH-mutant gliomas, which usually affect young people with a relatively long disease history and a quality of life impaired by neurological deficits, poor disease control, and toxicity related to other treatments, such as chemotherapy and radiation therapy.

Therefore, the INDIGO study represents a major turning point in the history of neuro-oncology, which has not witnessed new glioma treatments with comparable efficacy for more than 20 years, despite the many efforts in developing new therapeutics [1].

Importantly, notwithstanding its astonishing results, the INDIGO trial was restricted to a specific population and setting—chemoradiotherapy-naïve grade 2 IDH-mutant gliomas with residual or recurrent disease lacking contrast enhancement on MRI—and its positive outcomes need to be validated and generalized in future prospective studies. Vorasidenib and other IDH-mutant inhibitors have been and are currently under investigation, alone or as part of combination therapies, in other clinical settings and in grade 3 IDH-mutant gliomas [2, 3]. Whether the same results will be achieved in patients with less favourable characteristics (e.g. previous chemoradiotherapy, grade 3 and/or contrast-enhancing IDH-mutant gliomas) is presently a matter of heated discussion. To further complicate the picture, the findings from the INDIGO trial brought up the *vexata quaestio* of glioma: the lack of standardized and objective criteria for tumour grading results in high interobserver variability and poor specificity in classifying gliomas as grade 2 and 3, and this still represents a great issue that may severely affect patient eligibility and interpretation of clinical trials [4, 5].

In this complicated scenario, the identification of molecular and imaging biomarkers to predict response to IDH-mutant inhibitors, thus identifying patients who are going to benefit the most from the therapy, is warranted. Considering the proven success of IDH-mutant inhibitors and their expected rapidly growing use for the treatment of IDH-mutant gliomas, molecular imaging will have to face several challenges and answer new clinical questions in the next years to improve patient care in this setting. In particular, expected potential contributions are the non-invasive identification of IDH mutations and more objective tumour grading before surgery/biopsy, prediction of response to IDH-mutant inhibitors and thus better patient selection for the therapy, treatment response assessment and follow-up.

At present, radiolabeled amino acids are the most used PET radiopharmaceuticals for diffuse gliomas. Collectively, amino acid PET demonstrated value in the preoperative evaluation of the disease, grading and identification of most aggressive foci, differentiation of disease recurrence from treatment-related changes, and prognostication [6–8]. Importantly, some studies showed a relatively low sensitivity of amino acid PET in IDH-mutant gliomas, especially in grade 2 IDH-mutant astrocytomas [9]. Moreover, a major concern is represented by the challenging evaluation of treatment response in patients with amino acid PET-negative (i.e. "no measurable") diseases, as emerged in the recent report of the RANO group on PET-based response assessment criteria for diffuse gliomas (PET RANO 1.0) [10]. The main knowledge gap that needs to be urgently explored in future investigations is the capability of amino acid PET to predict and assess response in patients undergoing treatment with IDH-mutant inhibitors.

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On the other hand, in view of the limitations of amino acid tracers, the development of PET radiopharmaceuticals targeting the *IDH1* and *IDH2* mutations and thus enabling accurate detection of the mutant IDH1/2 enzymes is desirable and would play a fundamental role in the management of the many patients who will benefit from IDH-mutant inhibitors in the next future. IDH mutations-selective radiopharmaceuticals would be particularly useful in the setting of differential diagnosis of a suspected low-grade glioma, in the distinction of IDH-mutant and IDH-wildtype gliomas, in the determination of vital tumour tissue for treatment planning and discrimination of disease recurrence and treatment related changes, and for monitoring response to IDH-mutant inhibitors.

Few IDH mutations-selective tracers have been developed and tested in preclinical models [11–14]. In this issue of EJNMMI, Lai et al. [14] present results regarding the radiosynthesis of the radiolabelled IDH-mutant inhibitor [^{18}F] AG-120 (ivosidenib), providing valuable insights into its pharmacokinetic and metabolic properties in a mouse model of orthotopic glioma carrying the *IDH1* R132H mutation.

However, the optimal candidate for IDH-mutant glioma imaging is still to be found. Many efforts are needed to overcome the challenges for the development of IDH mutation-selective tracers, namely, the ability to cross the blood brain barrier, metabolic stability, and affinity and selectivity for mutant over wildtype IDH enzymes [15].

Finally, a long-term but exciting perspective is the potential of these agents for theranostic approaches.

In conclusion, IDH-mutant gliomas are still incurable tumours mainly affecting young people and associated with significant disability. After more than 20 years, the INDIGO trial has paved the way towards a novel therapeutic strategy and renewed hope among patients suffering from the disease.

The nuclear medicine and molecular imaging community must keep up with these changes and be prepared to face the new challenges provided by the recent advancements in the treatment of IDH-mutant gliomas.

Data availability Not applicable.

Declarations

Ethical approval Not applicable to this editorial.

Informed consent Not applicable.

Conflict of interest The authors declare no competing interests.

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