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Optimize treatment approaches in isocitrate dehydrogenase (IDH) mutant gliomas: open issues

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The 2021 update of the World Health Organization (WHO) Classification of Central Nervous System Tumors[1] has reinforced the integration of molecular data with conventional histological features for both diagnosis and treatment of diffuse gliomas. Mutations in isocitrate dehydrogenase (IDH) genes, IDH1 and IDH2, that represent an early event in gliomagenesis, are strong determinant of an improved overall survival in association with 1p/19q codeletion.

Thus, the WHO 2021 Classification recognizes WHO grade 2 and 3 IDH-mutant astrocytomas and IDH-mutant, 1p/19q codeleted oligodendrogliomas. Moreover, as CDKN2A/B homozygous deletion has been associated with shorter survival, its presence in an IDH-mutant astrocytoma will qualify the tumor as a WHO grade 4 regardless of a lower grade histological appearance.

In this issue of *Neuro-Oncology* Miller, Gonzalez Castro, and co-authors[2] have exhaustively and critically reviewed the state of art and future directions of diagnosis and management of IDH-mutant gliomas.

Overall, the WHO Classification 2021 has raised the issue of how to optimize and personalize standard and novel treatments in IDH-mutant gliomas. Supramaximal resection has been suggested to improve progression-free and overall survival in lower grade diffuse gliomas[3]; however, there is need to examine larger cohort of patients to see whether this is true for either IDH-mutant astrocytomas or IDH-mutant, 1p/19q codeleted oligodendrogliomas or both. The same question applies to reoperation, which is increasingly pursued: based on the more indolent natural course, one could hypothesize a higher relevance in IDH-mutant, 1p/19q codeleted oligodendrogliomas versus IDH-mutant astrocytomas in order to delay the need for radiotherapy and the risk of cognitive deficit in very long surviving patients. The role of adjuvant radiotherapy and chemotherapy for the new category of IDH-mutant astrocytomas with CDKN2A/B homozygous deletion, that represents a poorer prognostic group, needs to be defined: radiotherapy and adjuvant temozolomide, as demonstrated in the CATNON trial on anaplastic gliomas without 1p/19q codeletion, or radiotherapy with concomitant and adjuvant temozolomide, as in grade 4 IDH-wild type glioblastomas?

Another incompletely solved issue is the risk/benefit in the use of alkylating agents, in association with radiotherapy or alone, for the treatment of high-risk IDH-mutant gliomas. Temozolomide may lead to a hypermutation phenotype, associated with acquired defects in DNA mismatch repair genes, that seems inherently more aggressive.[4] Also, radiotherapy may result in homozygous deletion of the tumor suppressor gene CDKN2A and shorter survival time.[5] Thus far, all these concerns are out-weighted by the clear-cut improvement of survival following radio and/or chemotherapy. However, the risk of an acceleration of malignant transformation should be carefully monitored, especially in long surviving patients: in this regard the need of re-sampling tumor at time of progression to look for acquired molecular alterations driving an aggressive growth should be stressed.

Re-irradiation is increasingly used in tertiary centers, and new questions have arisen: does proton therapy offer advantages over photon therapy in critical areas (for instance in tumors close to hippocampus)? May carbon ions overcome the radio-resistance of recurrent tumors, due to the high linear energy transfer (LET)? Which will be the balance between increased tumor control and increased risk of damage to the normal brain?

Targeting IDH mutations is attractive due to an ubiquitous expression in tumor cells, retention during disease course and absence in normal brain cells.

Preclinical studies have shown the efficacy of IDH inhibitors in suppressing D-2-hydroxyglutarate (D-2HG), the oncogenic product of IDH mutation, and interfere with glioma growth.[6] However, it is still unclear whether D-2HG will keep the oncogenic potential over time.

The most interesting compound in an advanced phase of clinical investigation is vorasidenib, a first in class, dual inhibitor of mutant IDH1 and IDH2, developed for improved

penetration across the blood-brain barrier and shown to be active in an orthotopic model of IDH1-mutant glioma. A recent phase I trial has reported good tolerability, and 18% of partial + minor responses and a PFS of 36 months in a cohort of recurrent non-enhancing gliomas.[7] Now, we are awaiting the results of the phase III INDIGO trial (NCT04164901), investigating vorasidenib versus placebo in non-enhancing grade 2 IDH-mutant gliomas, who are progressive within 5 years of initial surgery and do not need radiotherapy and/or chemotherapy. A recent interim analysis for futility has suggested to go ahead with the study. In general, the most appropriate timing of use of mutant IDH inhibitors, alone or in combination with radiotherapy and/or chemotherapy, is an issue to be investigated in a near future. A promising approach is also to target the DNA hypermethylation, associated with IDH mutation, with demethylating agents. In addition to the production of oncogenic D-2HG, IDH1R132H mutation harbors a tumor-specific neo-epitope with high uniformity and penetrance, which is expressed in all tumor cells and preserved in recurrent tumors. A specific IDH1 vaccine has been shown to be able to elicit transient or sustained immune responses in 93% of treated patients with newly diagnosed astrocytomas.[8] As in IDH-mutant patients a suppression of T cell activity by D-2HG has been demonstrated, a randomized trial combining IDH-vaccine with the immune checkpoint inhibitor avelumab (AMPLIFY-NEOVAC) has been launched.

How to best monitor the response to IDH-mutant inhibitors? MR spectroscopy with specific sequences allows to quantify and measure D-2HG longitudinally, while on MRI volumetric assessments are preferred to the area assessments of RANO criteria.[9] Moreover, liquid biopsy of CSF to look for D-2HG levels seems promising.

Last, seizures prevail in IDH-mutant gliomas, and this is in part attributable to the similarity of D-2HG with glutamate, the main excitatory neurotransmitter. A recent research has demonstrated that IDH-mutant gliomas promote epileptogenesis through D-2HG-dependant m-TOR hyperactivation[10]: thus, a new avenue of combined treatment of epileptogenesis and tumor growth seems to open.

In conclusion, the optimization of the development of novel targeted drugs will require, in addition to advanced neuroimaging tools, the incorporation of surgical window-of-opportunity trials (phase 0) to better define the intratumoral distribution and confirm that the target is engaged.

Disclosure

Statement: The text is the sole product of the authors and no third party had input or gave support to its writing.

Conflicts of Interest

The author's conflicts of interest are: UCB, Novocure, Bayer, Genenta.

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