EBioMedicine 29 (2018) 9–10

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Methylation of PD-1 Promoter Gene as New Prognostic Marker for IDH Mutant Low-Grade Glioma?

Christine Marosi

Clinical Division of Medical Oncology, Department of Internal Medicine, Medical University of Vienna, Austria

In *EBioMedicine*, Röver et al. used a set of 419 low-grade glioma (LGG) patients from the TCGA database whose tumors showed a mutation in the isocitrate dehydrogenase 1 or 2 (IDHmt) to demonstrate that the promoters of the immune checkpoint genes PD-1, PD-L1, PD-L2 and CTLA-4 are differentially methylated within IDH mutated low-grade gliomas (LGG) (Röver et al., 2018). The authors showed that methylation of the PD-1 promoter provides a significant survival gain in patients with LGG (HR = 0.44 [0.30–0.66], $p < .001$) in combination with age (HR 3.83 [2.04–7.17], $p < .001$, whereas methylation of the promoters of the other immune checkpoint genes did not show prognostic impact. High PD-1 expression on the immune cells infiltrating the LGG is a marker for immune evasion, whereas PD-1 promoter methylation might promote active anti-glioma immune responses (Röver et al., 2018).

However, the biological significance of these findings remains unclear. There are methodological weak points related to the relatively low number of CPG sites for each of the genes examined such as on lacking correlations with known prognostic markers like 1p19q deletion and on the short follow-up of 24 months for LGG patients. The authors showed that their results add to the information provided by the G-CIMP status alone. The prognostic effect of PD-1 methylation is strong enough to be highly significant as early as after 2 years of follow-up. This opens a new field of investigation to answer questions about the significance of methylation of immune checkpoint inhibitors and their ligands – and potential therapeutic indications in LGG.

Using extensive immunohistochemical examinations, Berghoff et al. have shown that IDHmt LGG show higher PD-L1 expression and infiltration with cytotoxic immune cells than IDHwt LGG (Berghoff et al., 2017). These findings are in line with the findings of Amankulor et al. and Kohanbash et al., both showing a reduced immune infiltration by cytotoxic T cells in mouse models of IDHmt gliomas, as compared with IDHwt tumors (Amankulor et al., 2017; Kohanbash et al., 2017). Recently, using a sample of 120 patients with IDHmt LGG enrolled into the EORTC trial 22,033, Bady et al. showed that methylation of four DNA damage response genes predicts benefit from chemotherapy in IDHmt LGG (Bady et al., 2018).

Being diagnosed with an IDHmt LGG does not necessarily cause a threat of dying within the next few years, but profoundly impacts the quality of life of the affected person and his/her proxies. More than 70% of patients suffer from epileptic seizures, many complain about fatigue and according to tumor location, neurological deficits may develop. Only a minority of patients succeed to keep their professional life unchanged, most have to cut on their work load, work in less demanding positions or even lose their jobs. As LGG mostly affects people in the third or fourth decade of life, these restrictions hurt patients and their families during a period of maximal productivity and therefore also causes problems with childcare, partnership and financial outcomes (Boele et al., 2015).

Treatment of LGG is one of the most discussed topics and important challenges in neuro-oncology. LGGs are rare diseases, affecting <1/100,000 population per year. The available treatments for LGGs have been refined and improved during the last decades, but still consist of maximal safe neurosurgical resection which cannot be complete in patients with tumors in eloquent areas or stem ganglia, radiotherapy with a dose of 1.8 Gy/fraction to limit post-radiation deficits and chemotherapy based on alkylating agents, either dose-dense temozolomide (TMZ) or the combination of procarbacine, lomustine and vincristine (PCV). There were no other cytotoxic drugs, no targeted therapies or other drugs found effective in several decades of research so far. Radiotherapy as well as chemotherapy cause long-term toxicities (e.g., radionecrosis), cardiovascular events, cognitive deficits or second tumors after radiotherapy, hematologic toxicity up to secondary leukemias after chemotherapy. Watchful waiting to administer treatment at a time point when tumor progression was putatively causing more damage than the late toxicities has, for a long time, been a common practice for the management of patients with LGG.

However, the studies of the French glioma network demonstrated that most oligodendrogliomas show slow, but continuous growth of 3–4 mm/years, under the threshold of progression when the next scan occurs only a few months later, but resulting in significant growth when longer periods are considered (Mandonnet et al., 2010). To recruit patients with LGG into multicentric trials, criteria for “high risk” LGG were defined, mostly grouping patients aged 40 years or older, patients with a significant symptom burden, newly appeared neurological symptoms, increasing epileptic seizures resistant to the addition of anti-epileptic drugs, patients with tumors larger than 5 cm or crossing

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.01.016.
E-mail address: christine.marosi@meduniwien.ac.at (C. Marosi)

https://doi.org/10.1016/j.ebiom.2018.02.018

midline or with growth demonstrated by imaging (Buckner et al., 2016; Baumert et al., 2016). In 2016, two important trials focusing on the treatment of LGG high risk patients have been published, nevertheless leaving many open questions about treatment decisions in newly diagnosed LGG patients (Buckner et al., 2016; Baumert et al., 2016).

Nevertheless, the actual treatment strategies achieve "tumor containment", "survival with cancer", not a cure of the glioma, with reversibility of tissue damage and its neurological consequences. Potential advances besides the exploitation of immune-based strategies could include strategies against IDH-mutated cells as IDH mutation constitutes a very early event in the development of LGG, including either "repair" or bypassing of the mutation, or inhibition of the formation of the oncometabolite 2-hydroglutarate. Other potential strategies could consist in trying to destroy the network of microtubes building a glioma organoid within the brain, discovered recently by Osswald et al. (2015). This structure is tumor-specific and therefore a potential therapeutic target, probably also for immunotherapeutic approaches. Nevertheless, the glioma already has proven able to develop in an adult host.

There is still a long way to go to amend the therapeutic strategies in patients with LGG. We should be aware that successful new therapeutic strategies in LGG require long term collaboration of basic researchers and clinicians of many centers, as this disease is rare and the survival duration achieved with current therapy reached 14 years. Only combined multinational academic research will sustain this goal.

Disclosure

Nothing to declare.

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