2021 ESMO congress

343MO

Clinical features and DNA methylation patterns in long- and short-term survivors of WHO grade II-III glioma

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Background

WHO grade II-III gliomas affect rather young individuals and are characterized by a heterogenous survival prognosis ranging from months to years. Postoperative treatment prolongs survival but potentially impacts long-term quality of life and cognitive functioning. Therefore, refined prognostic stratification models are needed to guide future treatment studies.

Methods

Patients with histological diagnosis of WHO grade II/III glioma (lower-grade glioma, LGG) and treated in 2000 – 2018 at the Medical University of Vienna were identified. Short-term survivors (STS) were defined by OS < 12 months, while long-term survivors (LTS) were defined by OS > 10 years after diagnosis. Histological diagnosis according to the current WHO classification was done by a board-certified neuropathologist. DNA methylation profiling was performed using the Illumina EPIC 850k platform and methylation-based tumor classification was obtained using the Heidelberg Methylation Classifier.

Results

Among 599 LGG patients, 123 LTS (20.5%; 40/123 astrocytic, 44/123 oligodendroglial, 39/123 not otherwise specified or pre-WHO 2016 diagnosis = NOS) and 36 STS (6.0%, 24/36 astrocytic, 1/36 oligodendroglial, 11/36 NOS) were identified. At LGG diagnosis, Karnofsky Performance Scale (KPS) was lower ($p < 0.001$) and age was higher in STS as compared to LTS ($p < 0.001$). Epileptic seizures were more frequent in LTS, while motor deficits ($p < 0.001$), aphasia ($p = 0.025$) and visual disturbances ($p = 0.031$) were more common in STS at diagnosis. WHO grade II, *IDH* mutations, 1p19q codeletions and *MGMT* promoter methylation were each more frequent in LTS than in STS ($p < 0.001$). Unsupervised clustering of patient samples based on their methylome revealed 3 clusters. Cluster A included LTS with *IDH*-mutated tumors (n = 42, 68.9%). Cluster B was defined by STS with *IDH*-wildtype gliomas (n = 16, 26.2%). Cluster C comprised STS with *IDH*-mutated tumors (n = 3, 4.9%). Age, KPS and symptomatic burden did not differ between *IDH*-mutated tumors of clusters A and C ($p > 0.05$).

Conclusions

Our data indicate that DNA methylation profiling identifies *IDH*-mutated LGG with unfavorable prognosis. Further studies are needed to elucidate the pathobiology and optimal treatment of these high-risk LGG.

Legal entity responsible for the study

The authors.

Funding

Has not received any funding.

Disclosure

M. Preusser: Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Bayer; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Bristol-Myers Squibb; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Novartis; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Gerson Lehrman Group (GLG); Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: CMC Contrast; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: GlaxoSmithKline; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Mundipharma; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Roche; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: BMJ Journals; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: MedMedia; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: AstraZeneca; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: AbbVie; Financial Interests, Personal, Other, Lectures,

consultation or advisory board participation: Lilly; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Medahead; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Daiichi Sankyo; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Sanofi; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Merck Sharp & Dohme; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Tocagen; Financial Interests, Institutional, Funding: Boehringer Ingelheim; Financial Interests, Institutional, Funding: Bristol-Myers Squibb; Financial Interests, Institutional, Funding: Roche; Financial Interests, Institutional, Funding: Daiichi Sankyo; Financial Interests, Institutional, Funding: Merck Sharp & Dohme; Financial Interests, Institutional, Funding: Novocure; Financial Interests, Institutional, Funding: GlaxoSmithKline; Financial Interests, Institutional, Funding: AbbVie. A.S. Berghoff: Financial Interests, Personal, Research Grant: Daiichi Sankyo; Financial Interests, Personal, Research Grant: Roche; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Roche; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Bristol-Myers Squibb; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Merck; Financial Interests, Personal, Other, Lectures, consultation or advisory board participation: Daiichi Sankyo; Financial Interests, Personal, Funding, Travel support: Roche; Financial Interests, Personal, Funding, Travel support: Amgen; Financial Interests, Personal, Funding, Travel support: AbbVie. All other authors have declared no conflicts of interest.