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Clinical Implications of Molecular Neuropathology and Biomarkers for Malignant Glioma

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Abstract Malignant gliomas are currently diagnosed based on morphological criteria and graded according to the World Health Organization classification of primary brain tumors. This algorithm of diagnosis and classification provides clinicians with an estimated prognosis of the natural course of the disease. It does not reflect the expected response to specific treatments beyond surgery (eg, radiotherapy or alkylating chemotherapy). Clinical experience has revealed that gliomas sharing similar histomorphological criteria might indeed have different clinical courses and exhibit highly heterogenous responses to treatments. This was very impressively demonstrated first for oligodendrogliomas. The presence or lack of combined deletions of the chromosomal segments 1p/19q was associated with different benefit from radiotherapy and chemotherapy. We review current molecular markers for malignant gliomas and discuss their current and future impact on clinical neuro-oncology.

Keywords Glioma · Molecular diagnostics · Biomarker

Introduction

Malignant gliomas are a heterogeneous group of primary brain tumors. The entities are distinguished based on morphological criteria by histological analysis and presumed cell of origin. The World Health Organization (WHO) classification is a grading system integrating four ascending grades of malignancy. It is based on histomorphological criteria [1] but has been shaped by decades of clinical observation. The WHO classification reflects the anticipated malignancy of the tumor and serves as a criterion to estimate the prognosis of patients. However, clinical experiences derived from prospective randomized clinical trials indicate that histomorphological criteria alone might not be sufficient to predict clinical outcome. Gliomas even with identical histopathological features differ considerably regarding clinical course or response to therapy. Investigation of molecular genetics of the tumor may help to overcome some of these limitations. Moreover, the analysis of blood and urine for chemokines or enzymes as well as the monitoring of circulating cellular subtypes in the peripheral blood have emerged especially during the increasing repertoire of targeted therapies, notably antiangiogenic therapies [2].

Clinicians expect these molecular aberrations or changing expression levels in tumor tissue, blood, or urine ideally to serve as diagnostic, prognostic, predictive, or surrogate biomarkers. Molecular tumor characterization should also refine the histopathological WHO classification and hopefully extend it to allow predictions for specific therapeutic strategies. Biomarkers may help for easy and reliable identification of responders to a specific treatment, and allow identification of escape or resistance mechanisms during ongoing therapy. Several molecular markers have been characterized with respect to these clinical expectations. We review candidate molecules that have been investigated so far for anaplastic gliomas (WHO grade III) and for glioblastomas (WHO grade IV).

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O^6 Methylguanine DNA methyltransferase (MGMT)

The DNA repair protein MGMT rescues the DNA damage induced by alkylating chemotherapy (eg, lomustine or temozolomide) by removing the alkyl group from the O6 position of

guanine. During this repair process MGMT is irreversibly degraded and needs to be resynthesized de novo. As a consequence, the MGMT protein reservoir is potentially exhaustible. Early studies have examined the prognostic value of MGMT protein expression by immunohistochemistry and failed to consistently demonstrate a correlation with outcome. Of note, interobserver variation was also considerable [3]. The gold standard of protein determination in freshly isolated tumor tissue is of limited practical use, as it requires immediate processing of fresh tumor samples after surgery. Most recent studies analyzed the methylation of the *MGMT* gene promoter rather than protein levels or enzyme activity in glioma cells. Methylation of the gene promoter leads to silencing of transcription and thus lack of translation and absence of synthesis of functional protein. *MGMT* promoter methylation data consistently correlated better with clinical outcome than immunohistochemical evidence of MGMT protein in glioma tissue [3]. This might be due to the differential accuracy of the methods and to the fact that immunohistochemical MGMT detection precludes the precise distinction of MGMT-positive glioma cells from host-derived glioma-infiltrating non-neoplastic cells (eg, microglia) [4, 5]. In contrast, determination of *MGMT* promoter methylation using methylation-specific assays essentially detects an acquired abnormality thought to be derived exclusively from tumor cells.

An association of *MGMT* gene promoter methylation and the benefit from alkylating chemotherapy was investigated within the randomized pivotal European Organisation of Research and Treatment of Cancer (EORTC)—National Cancer Institute of Canada Clinical Trials Group (NCIC) phase III trial (EORTC 26981/22981-NCIC CE.3), which demonstrated improved survival when temozolomide was added to radiotherapy in newly diagnosed glioblastomas [6]. Methylation of the *MGMT* promoter in glioblastomas correlated with patients' benefit from adding temozolomide to radiotherapy [7] while there was little effect on progression-free survival in patients receiving radiotherapy alone. These data suggested that *MGMT* promoter methylation is rather a predictive marker of benefit from temozolomide in glioblastomas.

In an attempt to overcome MGMT-mediated resistance by dose-dense (21/28 days) temozolomide administration, the Radiation Therapy Oncology Group (RTOG)—EORTC Intergroup trial 0525 compared standard dosing regimen of temozolomide (5/28 days) dosage with dose-dense temozolomide after completion of radiotherapy and concomitant temozolomide. No difference in outcome (ie, progression-free or overall survival) was seen with no hint for a benefit from dose-intensified temozolomide in any subgroup of patients. Nevertheless, patients with *MGMT* promoter-methylated glioblastomas had a significantly superior overall survival (median, 23.2 months) compared to patients with unmethylated glioblastomas (median, 16 months) [8]. Recently, a study of the German Glioma Network analyzed *MGMT* promoter methylation in 233 elderly patients older than 70 years of age with glioblastomas (median age, 74 years) and correlated the MGMT status with patients' clinical outcome. Progression-free survival of patients with *MGMT*-methylated glioblastomas was longer when treated with radiotherapy plus temozolomide or temozolomide alone compared to patients receiving radiotherapy alone. On the other hand, patients with *MGMT*-unmethylated glioblastomas did not gain any significant survival benefit from temozolomide [9•]. Confirmation of these findings in prospective trials is needed to make individual treatment decisions based on the *MGMT* promoter methylation status. Specifically, it remains to be clarified whether elderly patients with *MGMT*-methylated glioblastomas should be treated with alkylating agent chemotherapy and deferred radiotherapy, while radiotherapy alone should be the treatment of choice for elderly patients with an *MGMT*-unmethylated promoter. Interestingly, treatment with alkylating agent therapy does not select for loss of *MGMT* methylation in glioblastoma, as has been determined by the German Glioma Network investigating *MGMT* promoter methylation in paired primary and recurrent glioblastomas [10•]. This finding is in line with the discovery of a mutator phenotype in *MGMT*-methylated glioblastoma after alkylating agent therapy allowing for selection of treatment-induced genetic alterations resulting in therapy resistance such as mutations in the *MSH6* gene, which is part of the mismatch repair pathway, that might also blunt the treatment efficacy of alkylating agents [11, 12•].

In the NOA-04 randomized trial, the impact of sequential treatments with chemotherapy or radiotherapy in patients with anaplastic gliomas was explored. Patients received radiotherapy or alkylating chemotherapy (ie, temozolomide or procarbazine, lomustine, and vincristine [PCV]) at initial diagnosis, and after progression chemotherapy or irradiation, respectively. There was no difference in overall outcome and the sequence of treatments did not matter. Overall, patients with a methylated *MGMT* gene promoter had a better outcome.

Interestingly, time to first treatment progression was comparable for both treatment arms even in the subgroup of patients with a methylated *MGMT* promoter, thus suggesting that in anaplastic gliomas the *MGMT* status is of prognostic value without prediction of benefit from alkylating agent chemotherapy [13]. This was confirmed in an EORTC trial demonstrating that *MGMT* promoter methylation was prognostic but not predictive for outcome to PCV in anaplastic oligodendrogliomas [14]. Thus, the predictive role of MGMT for benefit of temozolomide chemotherapy observed in glioblastomas cannot be extrapolated to other grades of glioma. Of note, methylation of the *MGMT* promoter is indicative of other associated alterations in anaplastic glioma predicting a superior clinical outcome notably co-deletion of 1p/19q and

mutations in the *isocitrate dehydrogenase (IDH)1* gene. This finding has been further clarified by the discovery of a glioma CpG island methylator phenotype (G-CIMP) present in over 45% of anaplastic glioma that was prognostic for outcome, and was highly correlated with *IDH1* mutations, 1p/19q co-deletions, and *MGMT* methylation [15]. Originally, G-CIMP was discovered in glioblastoma when screening 272 glioblastoma samples from The Cancer Genome Atlas (TCGA) project for genome-wide DNA methylation by Noushmehr et al. [16]. In glioblastoma, G-CIMP is infrequent, present in less than 10% of the cases, and strongly associated with mutations of *IDH1* and with superior clinical outcome. Subsequent studies suggest that *IDH1* mutations and, therefore, also G-CIMP, identify secondary glioblastoma that progress from lower-grade lesions. These findings have elucidated the evolution of gliomas, pathogenetically clearly separating primary glioblastoma from secondary glioblastoma and lower-grade gliomas. Thus, in future prospective randomized clinical trials, stratifications for the methylator phenotype and/or *IDH* mutations should be considered. Further, studying cancer-relevant pathways affected by the methylator phenotype may reveal novel promising drug targets.

Currently ongoing clinical trials for glioblastomas patients use the *MGMT* gene promoter methylation status as selection criterion for study inclusion (Fig. 1) or stratification factor. Studies selecting *MGMT*-methylated patients only, expect a synergistic effect of their novel agent with temozolomide treatment. In contrast, selecting *MGMT*-unmethylated glioblastoma patients, allows omission of temozolomide. This allows testing of new drugs with a different mode of action and provides the opportunity to develop new treatment strategies to improve the outcome in these patients who gain less benefit from the current standard of care.

Combined Deletions of Chromosomes 1p and 19q

Investigations using microsatellite markers identified a frequent combined loss of heterozygosity (LOH) on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) in malignant gliomas [17]. This combined loss is now commonly referred to as 1p/19q co-deletions and usually affects the whole chromosomal arms that seems to be mediated by a t(1;19)(q10;p10). Interestingly, this combination of LOH is almost never found in any non-glial malignancy. Moreover, 1p/19q co-deletions are commonly associated with oligodendroglial differentiation. Histological evidence of an oligodendroglioma or at least an oligodendroglial component in a mixed glioma is virtually always coupled with an *IDH1/2* mutation [18]. Patients with oligodendroglioma that harbor 1p/19q deletions have superior outcome after radiotherapy and chemotherapy [19]. In glioblastomas, on the other hand, 1p/19q deletions are rare and do not predict prognosis of patients [20].

The identification of frequent 1p/19q co-deletions in malignant gliomas and the clinical relevance of this finding for predicting response to therapy of oligodendroglioma patients indicated the presence of tumor suppressor genes or other genes with important roles for radiotherapy- or chemotherapy-induced cell death in these chromosomal regions. Recently, candidate genes have been identified by exome sequencing (sequencing of all coding exons).

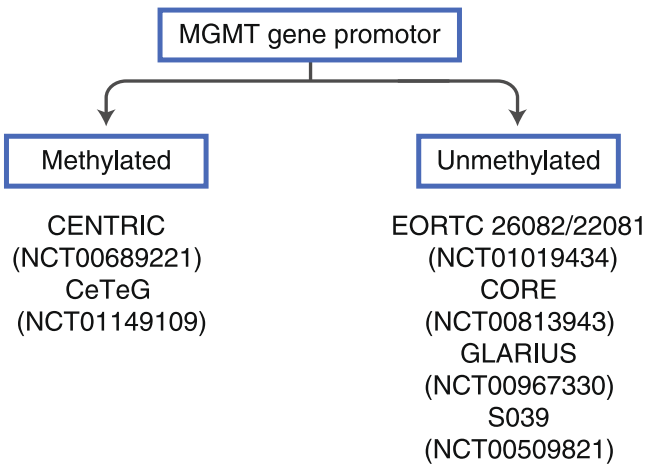

Fig. 1 Enrollment into clinical glioblastomas trials based on MGMT methylation status. *CENTRIC*, addition of cilengitide to standard therapy compared with standard treatment in newly diagnosed glioblastomas (*recruitment completed*). *CeTeG*, addition of lomustine to standard therapy compared with standard treatment in newly diagnosed glioblastomas (*recruitment ongoing*). *EORTC 26082/22081*, temsirolimus plus radiotherapy compared with standard treatment in newly diagnosed glioblastomas (*recruitment ongoing*). *CORE*, standard therapy with cilengitide either twice weekly or five times per week versus standard therapy in newly diagnosed glioblastomas (recruitment ongoing), *GLARIUS*, bevacizumab and irinotecan versus standard therapy in newly diagnosed glioblastomas (*recruitment ongoing*), *S039*, enzastaurin before and concomitant with radiotherapy followed by enzastaurin maintenance in newly diagnosed glioblastomas (*recruitment completed*). The ClinicalTrials.gov identifier numbers are indicated in the figure

Mutations have been identified in *CIC*, a homolog of the *Drosophila* gene *capicua*, on chromosome 19q, and the *FUBP1* gene (far upstream element binding protein 1), on chromosome 1p [21]. The functional roles of CIC and FUBP1 in the pathogenesis of these tumors are currently under investigation.

Currently ongoing clinical trials include patients with anaplastic gliomas only after determination of 1p/19q status (eg, CATNON trial [NCT00626990] or the CO-DEL trial [NCT00887146]), further emphasizing the impact of this genetic marker for clinical neuro-oncology.

Isocitrate Dehydrogenase

Somatic mutations of the *IDH1* gene were identified by a whole-genome mutational analysis in glioma tissue samples [22]. The mutations occur at codon 132 of the *IDH1* gene, and less frequently at corresponding codons of *IDH2* [22, 23], and were found in about 60% to 80% of astrocytomas and oligodendrogliomas of grades II and III but in less than 10% of glioblastomas. In glioblastomas, the presence of *IDH1* mutations likely identifies secondary glioblastomas that originate from a prior lower-grade glioma [24]. This biomarker reliably identifies patients with a more favorable prognosis independent of treatment [13, 25, 26].

The neomorphic IDH mutants give rise to the production of D-2-hydroxyglutarate (2-HG) that accumulates to high levels in glioma [27]. The oncometabolite 2-HG is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases, reducing the activities of the families of histone demethylases and TET 5-methylcytosine hydroxylases, including the tet oncogene family member TET2, resulting in widespread epigenetic changes. Interestingly, in acute myeloid leukemia (AML), *IDH1* and *IDH2* mutations are also associated with a methylator phenotype, and were shown to be mutually exclusive with loss-of-function mutations in the *TET2* gene. These observations suggests a functional link between *IDH1/2* mutations, the production of 2-HG, and the development of a methylator phenotype in glioma and AML (ie, metabolism meets epigenetics) [28••, 29]. The concentrations of the oncometabolite 2-HG in the blood can be used to monitor disease activity in patients with AML. However, 2-HG levels in the serum of glioma patients are not suitable as surrogate markers. The levels do not correlate with the presence of *IDH1* or *IDH2* mutations in the glioma tissue nor with tumor size [30]. This might be due to the fact that in contrast to AML, the actual tumor site is not the blood but the brain. This might account for too low concentrations in peripheral blood of glioma patients. Of note, concentrations of 2-HG in the cerebrospinal fluid have not yet been analyzed for 2-HG levels. Currently, efforts aim at detecting 2-HG by magnetic resonance spectroscopy that would provide a noninvasive diagnostic tool to identify *IDH1/2* mutant gliomas [31].

Recently, an antibody has been developed recognizing the mutant IDH1-R132H protein [32], which accounts for over 90% of all mutations in glioma. The development of this antibody has facilitated the widespread use of this marker, the rapid acquisition of data, and correlation with clinical outcome. The survival of patients with *IDH1*-mutant astrocytomas or oligodendrogliomas of grades II-III and including glioblastoma is longer than that of their IDH wild-type counterparts. Importantly, overall survival of patients with IDH1-mutated glioblastomas (WHO grade IV) is better than for patients with IDH1 wild-type anaplastic astrocytomas (WHO grade III) [33], confirming the potential of molecular markers to improve outcome prediction and clinical utility of the WHO classification.

IDH status reliably identifies patients with a more favorable prognosis but does not predict treatment-specific responses of glioma patients [13, 34, 35••, 36–38], at least according to currently available data, and has not yet led to novel treatment strategies for malignant gliomas. In the future, clinical trials with IDH1 status as enrollment criteria might help to further define the impact of this molecular feature on clinical neuro-oncology. Given the fact that the antibody is already available for neuropathological histology diagnostics, it might be even easier to call for an upfront IDH1 status before enrollment into clinical trials than for an MGMT status. For example, a possible strategy might be to exclude glioblastoma patients with *IDH* mutations from future glioblastoma trials.

Epidermal Growth Factor Receptor

Amplifications of epidermal growth factor receptor (EGFR) are frequent in primary glioblastomas [11, 20]; overexpression of EGFR has been associated with shorter survival in glioblastoma. Several compounds targeting EGFR are available for clinical use, and have also been evaluated in malignant glioma. Neither of these demonstrated satisfying antiglioma activity, although bioavailability and activity to dephosphorylate the EGFR in the tumor tissue could be shown for gefitinib in a phase II trial [39•]. The prospective randomized phase II EORTC 26034 trial on erlotinib in unselected recurrent glioblastoma did not demonstrate any evidence for antitumor activity [40]. A recent randomized trial investigated afatinib, a high-affinity irreversible EGFR tyrosine kinase inhibitor, versus dose-dense temozolomide (21/28 days) alone or the combinations of both. Again, no evidence of antitumor activity of EGFR inhibition could be shown [41]. Currently, the EGFR status does not impact clinical practice in neuro-oncology in any direction. The EGFRvIII mutation, a specific subtype of EGFR mutations,

might be used in the future for selecting patients for clinical trial enrollment. This specific mutation encodes for a constitutively active receptor and might be a useful target for immunotherapy [42].

Circulating Biomarkers

The investigation of circulating molecules or cells in peripheral blood and urine in patients with malignant gliomas has regained attention by the emergence of several antiangiogenic compounds. None of these parameters have entered routine clinical practice decision making yet. In a phase II trial investigating cediranib in patients with recurrent glioblastomas, plasma and urine were collected at baseline and at several defined time points after start of study medication. Increased levels of metalloproteinase 2 in plasma and increased levels of metalloproteinase 9 in urine were correlated with poor progression-free survival, whereas increased plasma levels of placental growth factor and basic fibroblast factor were correlated with longer overall survival. Increased plasma levels of stromal-derived factor 1, soluble vascular growth factor receptor 1, and soluble Tie 2 were correlated with radiographic tumor progression [2]. The value of circulating biomarkers still needs to be further defined in future clinical trials.

Conclusions

Biomarkers are an emerging field also for neuro-oncology. Considerable progress has been made in identifying, characterizing, and applying molecular markers. These efforts will certainly refine the current histomorphologically based WHO classification in the future. In the present daily clinical decision making for the treatment of patients with malignant gliomas, however, molecular markers are barely used. The lack of better strategies for *MGMT*-unmethylated patients and limitations of accurate determination of the MGMT status limit its applicability in daily practice outside clinical trials. Deletion of 1p/19q allows identification of a prognostically more favorable subgroup; the ongoing randomized clinical trials will determine whether this allows one to adapt the treatment strategy individually. As outlined above, the identification of the IDH1 status demonstrates that this molecular aberration can be used to amend and refine the existing WHO classification. The recognition of IDH-mutated secondary glioma as a distinct pathogenetic entity will therefore very likely influence the next revision of the WHO classification. On the other hand, currently ongoing powerful high-throughput analyses will most probably identify novel so-far unknown candidate molecules that could potentially serve as biomarkers for malignant gliomas. Yet, the identification of new markers will hopefully be paralleled by the identification of new drugs for the treatment of patients with malignant gliomas.

Disclosure Conflicts of interest: G. Tabatabai: has received honoraria for advisory boards from MSD and Roche.; M. Hegi: is a consultant for Merck Serono, MDxHealth, and MSD; has received honoraria for lectures or advisory boards from Merck Serono, MDxHealth, Shering Plough/MSD, and Roche; and has received grant support from AstraZeneca; R. Stupp: has served on and received honoraria for advisory boards to Merck Serono (EMD), MSD (Merck & Co), Roche, and MDxHealth; M. Weller: has received research grants from Merck Serono and Roche and honoraria for lectures or advisory boards from Magforce, MSD, Merck Serono, and Roche.

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