Personalized care in neuro-oncology coming of age: why we need MGMT and 1p/19q testing for malignant glioma patients in clinical practice

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Histological subtyping and grading by malignancy are the cornerstones of the World Health Organization (WHO) classification of tumors of the central nervous system. They shall provide clinicians with guidance as to the course of disease to be expected and the choices of treatment to be made. Nonetheless, patients with histologically identical tumors may have very different outcomes, notably in patients with astrocytic and oligodendroglial gliomas of WHO grades II and III. In gliomas of adulthood, 3 molecular markers have undergone extensive studies in recent years: 1p/19q chromosomal codeletion, O6-methylguanine methyltransferase (MGMT) promoter methylation, and mutations of isocitrate dehydrogenase (IDH) 1 and 2. However, the assessment of these molecular markers has so far not been implemented in clinical routine because of the lack of therapeutic implications. In fact, these markers were considered to be prognostic irrespective of whether patients were receiving radiotherapy (RT), chemotherapy, or both (1p/19q, IDH1/2), or of limited value because testing is too complex and no chemotherapy alternative to temozolomide was available (MGMT). In 2012, this situation has changed: long-term follow-up of the Radiation Therapy Oncology Group 9402 and European Organisation for Research and Treatment of Cancer 26951 trials demonstrated an overall survival benefit from the addition to RT of chemotherapy with procarbazine/CCNU/vincristine confined to patients with anaplastic oligodendroglial tumors with (vs without) 1p/19q codeletion. Furthermore, in elderly glioblastoma patients, the NOA-08 and the Nordic trial of RT alone versus temozolomide alone demonstrated a profound impact of MGMT promoter methylation on outcome by therapy and thus established MGMT as a predictive biomarker in this patient population. These recent results call for the routine implementation of 1p/19q and MGMT testing at least in subpopulations of malignant glioma patients and represent an encouraging step toward the development of personalized therapeutic approaches in neuro-oncology.

Keywords: gliomas, IDH-1, MGMT, 1p/19q, prognosis.

The World Health Organization (WHO) classifies tumors of the CNS by histological criteria, assigning them a presumed histogenetic origin and, depending on certain cytological and histological features of anaplasia, grades of I to IV, corresponding to...
degrees of malignancy defined by the expected clinical course. The WHO classification has assumed fundamental clinical relevance, since its histopathological categorization determines how the neuro-oncologist manages an individual patient after surgery, by watchful waiting or with radiotherapy (RT), chemotherapy, or both. Progress in molecular diagnostics has allowed the identification of a number of markers and profiles that identify subtypes of gliomas. Repeatedly these molecular markers have been validated in prospective clinical trials. Molecular marker determination is technically demanding and requires reproducible and validated test procedures. However, molecular tumor characterization becomes more and more necessary in the majority of cases in order to make educated and state-of-the-art individualized treatment decisions. While the currently used 4th edition of the WHO classification, published in 2007, is purposely limited to traditional anatomopathological criteria, any future revision will need to implement also molecular markers for adequate histological diagnosis. The current classification lumps together tumor types of identical morphological appearance, while both natural clinical course and different responses to treatment, as well as molecular profiling, indicate distinct entities. Further, histopathological diagnoses remain subjective and prone to significant interobserver variation, especially in grades II and III glioma.

Molecular markers have turned out to be powerful aids for estimating clinical outcomes for certain brain tumors. The potential value of molecular markers thus is to aid in the differential diagnosis of brain tumors that are difficult to distinguish based on histology alone, to estimate outcome within histologically defined tumor entities, and ultimately to predict benefit from specific types of therapy.

Conceptionally, the differentiation between prognostic and predictive factors in the field of gliomas is difficult. Prognostic is meant to signify an effect on outcome that is independent of therapeutic interventions, but the vast majority of patients receive different treatments during the course of their disease. Predictive signifies that a marker allows prediction of benefit specifically from one type of treatment rather than another. The correct understanding of prediction versus prognostication becomes particularly relevant in the discussion of the respective roles of using status of 1p/19q, O6-methylguanine methyltransferase (MGMT), and isocitrate dehydrogenase (IDH) 1/2 to estimate benefit from alkylating agent therapy. Here we discuss the increasing impact and state of the art of these 3 molecular markers for gliomas of adulthood in clinical practice and outline why we believe that testing for these markers should become standard practice based on recent data from large randomized clinical trials (Tables 1 and 2, Fig. 1).

1p/19q Codeletion

Combined loss of genetic material from chromosomal arms 1p and 19q has long been recognized as a typical molecular signature of oligodendrogial tumors and results from an unbalanced translocation that leads to
the loss of one hybrid chromosome and thereby loss of heterozygosity. The association of this molecular marker with brain tumor formation led to an extensive search for tumor suppressor genes located in these genomic regions, but the first promising candidate genes have only recently been identified by exome sequencing. Most oligodendrogliomas with 1p/19q codeletion indeed carry mutations in the CIC gene, a homolog of the Drosophila gene capicua, located on 19q13.2. A smaller subset of these tumors carries mutations in the FUBP1 gene, which encodes the “far upstream element binding protein” on chromosome 1p. However, the biological role of these mutations remains to be elucidated.

Three randomized clinical trials have demonstrated that anaplastic glioma patients with 1p/19q codeleted tumors live longer when receiving RT or alkylating agent chemotherapy or both.

In trial 9402 of the Radiation Therapy Oncology Group (RTOG), 289 patients with anaplastic oligodendroglioma or anaplastic oligoastrocytoma confirmed at central pathology review were randomized to neoadjuvant procarbazine/CCNU/vincristine (PCV) chemotherapy followed by RT (PCV \rightarrow RT) versus RT alone. Status of 1p/19q was assessed centrally by fluorescence in situ hybridization (FISH), and 93/201 (46%) tested patients demonstrated combined loss. Although there was no formal crossover design, 80% of the patients randomized initially to RT alone received chemotherapy at progression. An initial analysis after a minimum follow-up of 3 years showed a median progression-free survival (PFS) of 2.6 years for PCV \rightarrow RT compared with 1.7 years for RT alone (P = .004); however, median overall survival (OS) was similar: 4.9 years with PCV \rightarrow RT versus 4.7 years with RT alone (P = .26). The absence of a survival benefit and the occurrence of severe (grade 3 or 4) toxicity in 65% of the PCV-treated patients were felt to outweigh the moderate gain in PFS. Median OS was longer in cases of 1p/19q codeleted tumors than in cases of tumors lacking this aberration (>7 y vs 2.8 y, P < .001). However, there was no significant effect of type of treatment on survival by 1p/19q status. In patients with 1p/19q codeleted tumors, median OS was not reached with PCV \rightarrow RT and was reached at 6.6 years with RT alone (P = .28). For the other patients, median OS was reached at 2.7 versus 2.8 years with versus without PCV (P = .33). Yet, at extended follow-up in 2012, these conclusions needed to be revoked. In patients with tumors lacking 1p/19q codeletions, median OS was still similar at 2.6 years for PCV \rightarrow RT versus 2.7 years for RT alone (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.58–1.23; P = .39). However, 126 patients

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Fig. 1. Exemplary results obtained by commonly used methods for the assessment of molecular markers in gliomas. (A) 1p/19q codeletion. Left panel: PCR analysis for loss of heterozygosity (LOH) at microsatellite markers on 1p (D1S2696) and 19q (D19S572) in a glioblastoma (GBIV) and in an anaplastic oligodendroglioma (AOIII). Note LOH at both markers (arrowheads) in the tumor DNA (T) as compared to the patient’s blood DNA (B) in the AOIII but not in the GBIV. Right panel: Demonstration of 1p and 19q codeletion by FISH in an oligodendroglioma (FISH images were kindly provided by Dr David Capper, Heidelberg). Dual color probe sets detecting loci on 1p23 (red) and 1q25 (green) or 19q13 (red) and 19p13 (green) were used and nuclei were counterstained with 4’,6-diamidino-2-phenylindole (blue). Note that most nuclei show 2 green signals with the reference probes but only 1 red signal with the 1p23 or 19q13 probes. (B) IDH1 mutation. Left panel: diffuse astrocytoma with immunostaining of tumor cells for R132H mutant IDH1 protein, Right panel: pyrogram (reverse sequence) indicating a heterozygous C-to-T point mutation at nucleotide 394 of the IDH1 gene (arrow) resulting in a missense mutation at codon 132 (c.394C>T, R132C) in another case of diffuse astrocytoma. (C) MGMT promoter methylation. Upper panel: Methylation-specific PCR for unmethylated (U) and methylated (M) promoter sequences in 3 GBIVs, a no template control, the glioblastoma cell line A172 with a methylated MGMT promoter, and peripheral blood cells with an unmethylated MGMT promoter. Tumor 1 lacked MGMT promoter methylation, while tumors 2 and 3 had MGMT methylated promoters. Bottom panel: MGMT promoter methylation analysis by pyrosequencing of sodium bisulfite–modified DNA extracted from a GBIV. The mean percentage of methylation at the individual CpG sites (arrows) is noted in the blue boxes on top of the pyrogram.
with 1p/19q codeleted tumors had median OS of 14.7 years with PCV → RT versus 7.3 years with RT alone (P = .03), translating into an HR of 0.59 (95% CI, 0.37–0.95; P = .03). This difference in OS was observed despite reoperation rates that were similar in both arms (43% with PCV → RT vs 54% with RT alone) and salvage chemotherapy that was more frequently administered in the RT-alone arm (57% vs 81%).12

The European Organisation for Research and Treatment of Cancer (EORTC) 26951 trial, which was similarly designed to the RTOG trial and somewhat larger, was initially reported in 2006 and updated at the 2012 plenary session of the American Society of Clinical Oncology. A total of 368 patients with locally diagnosed anaplastic oligodendroglioma or anaplastic oligoastrocytoma were randomized to RT or RT followed by PCV (RT → PCV). A subgroup of 78 patients (21%) demonstrated 1p/19q codeletions as assessed by FISH. Again, the addition of PCV after RT increased PFS (23 vs 13.2 months, P = .0018), but median OS at a median follow-up of 60 months was similar (40.3 vs 30.6 months, P = .23). There was also no specific effect of treatment when split by 1p/19q status: for patients with 1p/19q codeleted tumors, median OS was not reached with either RT → PCV or RT alone, while for patients whose tumors had a partial or no deletion, median survival times were 25.2 and 21.4 months for RT → PCV and RT alone, respectively.10 The 2012 update demonstrates a survival advantage for early adjuvant PCV chemotherapy in patients with codeleted tumors. With now long-term median follow-up of >10 years, median survival has still not been reached in the subgroup of 42 patients with codeleted tumors and initially receiving RT → PCV, compared with a median survival of 9.3 years for the 38 patients who initially received RT alone, and frequently received chemotherapy only at progression (P = .059). Also in concordance with the RTOG results, median OS for patients without codeleted tumors was still similar, with 25 months for RT → PCV versus 21 months for RT alone (P = .19).13

The German Neuro-Oncology Group trial NOA-04 randomized 318 patients with anaplastic astrocytoma, anaplastic oligodendroglioma, and mixed anaplastic oligoastrocytoma, after biopsy or resection, 2:1:1 to receive RT, PCV, or temozolomide (TMZ), all as single modality treatment. At unacceptable toxicity or progression, patients randomized to RT were further randomized to PCV or TMZ, whereas patients randomized to chemotherapy were to receive RT. Histology was centrally confirmed before randomization, and 23% (74 patients) had 1p/19q codeletion by FISH. The primary endpoint was treatment failure, defined as death, progression after RT and one line of chemotherapy, or ineligibility for salvage at first relapse, with PFS and OS as secondary endpoints. At first analysis after a maximum follow-up of 54 months, when 43% of patients had reached the primary endpoint of treatment failure, RT and chemotherapy induced (i) similar PFS, (ii) similar time to treatment failure, and (iii) similar OS across all histologies. The 1p/19q codeletion was again a favorable prognostic factor, translating into a risk reduction of approximately 50%, which was independent of treatment arm.11 The current long-term data of the RTOG 9402 and EORTC 26951 trials suggest that the follow-up of NOA-04 is still too short to allow an estimate of a predictive value of 1p/19q status for benefit from RT alone versus chemotherapy alone. Moreover, crossover at progression will impact the survival endpoint in NOA-04.

In glioblastomas, 1p/19q codeletions are rare and of unknown biological significance.14 Patients with WHO grade II gliomas do not always receive RT or chemotherapy after the first surgical intervention. Such patients treated with surgery alone allow estimation of whether the 1p/19q codeletion specifically mediates increased responsiveness to RT or alkylating agents or whether these tumors take a less aggressive course even in the absence of genotoxic treatment. Small retrospective studies indeed indicate no difference in time to reintervention in patients with WHO grade II gliomas managed by surgery alone by 1p/19q status,15,16 lending support to the hypothesis of specific therapy sensitivity conferred by 1p/19q codeletion. However, 2 French series reported slower growth rates in 1p/19q codeleted low-grade gliomas.17,18 Future studies need to determine the mechanistic roles of the CIC or FUBP1 genes that seem to be targeted by mutation and 1p/19q codeletion in association with increased sensitivity to RT and alkylating agent chemotherapy in 1p/19q codeleted oligodendrogliomas.

Accordingly, 1p/19q codeletion predicts longer OS when glioma patients receive RT or chemotherapy alone or their combination, but the long-term follow-up of 2 randomized trials strongly suggests a survival benefit of initial combined modality treatment using PCV plus RT over RT alone in patients with 1p/19q codeleted tumors.12,13 These observations have important implications for ongoing clinical trial activities and for clinical practice. Based on the data from RTOG 9402, the CODEL trial (NCT 00887146) has been suspended because RT alone is no longer considered appropriate for patients with 1p/19q codeleted anaplastic oligodendrogial tumors. Whether the neuro-oncology community will accept the old PCV regimen added to RT as a new standard of care in patients with these tumors is also uncertain at present.

**MGMT Promoter Methylation**

MGMT is a DNA repair protein that removes the alkylating agent of the O6 position of guanine, the most cytotoxic lesion induced by alkylating agent chemotherapy. An association of MGMT expression or activity and the benefit from alkylating agent chemotherapy in glioma patients was reported 15 years ago.19,20 The molecular modification associated with loss of MGMT expression is aberrant methylation of the MGMT promoter region, leading to gene silencing and consequently reduced proficiency to repair DNA damage induced by alkylating agent chemotherapy. In the pivotal trial of TMZ for newly diagnosed glioblastoma,21 MGMT promoter methylation was strongly associated with the extent of benefit from the addition of TMZ in the experimental
arm but had only minor prognostic impact for PFS in patients receiving initial RT alone, suggestive of a predictive effect. It is now widely accepted that MGMT status can be reliably tested using a standardized methylation-specific PCR, while validation of clinical use for other assays is lacking. MGMT status is homogeneous within individual tumors and, for glioblastomas, is retained in recurrent tumors.

The strong prognostic role of MGMT promoter methylation was confirmed prospectively in the RTOG 0525/EORTC/North Central Cancer Treatment Group Intergroup Study using a centralized quantitative methylation-specific PCR assay. The study compared 3 weeks on, 1 week off adjuvant dose-intensified TMZ with the standard TMZ regimen. OS was 23.2 months in patients with MGMT promoter-methylated tumors versus 16 months in patients unmethylated tumors.

A predictive, as opposed to a prognostic, role of MGMT status can be assessed particularly well in patients receiving either RT or chemotherapy alone versus the combination. Such single modality treatments are often administered to elderly patients where the combined modality may be less active or less well tolerated or both. In an unselected sample of 233 glioblastoma patients aged $\geq$70 years, median DFS was 4.8 months and median OS was 7.7 months. For the whole cohort, DFS was 5.2 versus 4.7 months and OS was 8.4 versus 6.4 months in patients with versus without MGMT promoter methylation. Patients with MGMT promoter-methylated tumors had longer DFS when receiving RT plus chemotherapy or chemotherapy alone compared with patients receiving RT alone. Patients with MGMT promoter-unmethylated tumors appeared to derive no survival benefit from chemotherapy, regardless of whether given at diagnosis together with RT or as a salvage treatment. A similar conclusion was reached in a French study of elderly glioblastoma patients. The conclusion that MGMT promoter methylation may indeed be a useful predictive biomarker to stratify elderly glioblastoma patients for RT versus alkylating agent chemotherapy has now been established in 2 prospective randomized trials, the NOA-08 trial and the Nordic trial.

NOA-08 randomized patients with glioblastoma ($n = 331$) or anaplastic astrocytoma ($n = 40$) aged 66 or more to RT alone or one week on one week off dose-intensified TMZ alone and sought to demonstrate non-inferiority of TMZ compared with RT. Median DFS and OS did not differ between arms. MGMT promoter methylation was associated with prolonged OS of 11.9 versus 8.2 months. More importantly in the context of molecular signatures, patients with MGMT promoter methylation had longer DFS when treated with TMZ (8.4 vs 4.6 months), whereas patients without MGMT promoter methylation had longer DFS when receiving RT (4.6 vs 3.3 months).

In the Nordic trial, newly diagnosed glioblastoma patients aged 60 years of age were randomized to standard RT (60 Gy) versus hypofractionated RT (34 Gy over 2 wk) versus TMZ (200 mg/m$^2$ days 1–5 every 28 days for 6 cycles). OS with standard RT was inferior to that with TMZ and hypofractionated RT. MGMT promoter methylation was associated with significantly better OS in TMZ-treated patients (9.7 vs 6.8 months; 95% CI, 8.0–11.4 vs 5.9–7.7; HR, 0.56; 95% CI, 0.34–0.93; $P = .03$) but not in RT patients (8.2 vs 7.0 months; 95% CI, 6.6–9.9 vs 5.7–8.3; HR, 0.97; 0.69–1.38; $P = .88$). Accordingly, these consistent trial results are practice changing, and elderly glioblastoma patients eligible for either RT or TMZ should undergo MGMT testing prior to clinical decision making.

Furthermore, MGMT promoter methylation was associated with potential benefit from the integrin antagonist cilengitide in patients of newly diagnosed glioblastoma. If this is confirmed in the ongoing phase III registration trial (CENTRIC, NCT 00689221), MGMT status determination will have direct implication in the choice of treatment for all patients and will be required routinely.

Interestingly, this powerful predictive value of MGMT status in glioblastoma was not observed in 2 randomized trials in anaplastic glioma patients. NOA-04 reported a strong positive prognostic effect of MGMT promoter methylation for DFS in patients receiving either RT or alkylating agent chemotherapy, with no evidence for preferential activity of chemotherapy in MGMT promoter-methylated patients. Similarly, the EORTC 26951 trial observed the same extent of DFS advantage in patients with tumors with MGMT promoter methylation receiving either RT alone or RT + PCV. This observation, which at first glance is paradoxical, may be explained by the fact that despite similar clinical and radiological presentations, WHO grades III and IV glioma are distinct entities with different pathogeneses and prevailing tumorigenic pathways. It is tempting to conclude that this difference may be due to the different biology of IDH1/2 mutant tumors, in particular its association with the cytosine–phosphatidyl–guanine (CpG) island methylator phenotype (CIMP), which dominates grade III anaplastic tumors versus IDH1/2 wild-type tumors, which dominate grade IV primary glioblastomas.

In fact, CIMP-positive grade II and III gliomas almost invariably harbor a methylated MGMT promoter, while CIMP-negative gliomas regardless of tumor grade display an MGMT methylation frequency of approximately 50%.

### IDH1/2 Mutations

Mutations of IDH1 and 2 genes are common and characteristic molecular lesions in grades II and III gliomas. The IDH1 gene encodes cytosolic IDH1, whereas the IDH2 gene encodes mitochondrial IDH2. The development of an antibody recognizing the mutant IDH1R132H protein, the most common IDH1 mutant in gliomas, facilitated the rapid implementation of IDH1 assessment within routine diagnostic neuropathology. IDH mutations cluster at codon 132 of IDH1 and codon 172 of the IDH2 gene, suggesting that they confer a gain of function to the mutant enzymes. Mutant IDH proteins exhibit altered substrate specificity resulting in increased production of D-2-hydroxyglutarate, which acts as an oncometabolite, instead of α-ketoglutarate, which is produced by wild-type IDH enzymes.
contrast to other molecular markers in gliomas, D-2-hydroxyglutarate may be used as a biomarker also for monitoring the natural course of disease and response to therapy. While D-2-hydroxyglutarate levels may be too low in the serum of IDH1/2 mutant glioma patients to be of diagnostic value, it may become possible in the future to monitor local, tumor-associated mutant IDH1/2 activity using MR spectroscopy for the detection of D-2-hydroxyglutarate.

Serial stereotactic biopsies revealed a homogeneous pattern of IDH1 status within gliomas of WHO grades II and III, even within and outside of anaplastic foci. In most glioma entities, patients with IDH mutant tumors show longer OS than those with IDH wild-type tumors; in fact, OS in patients with WHO grade IV glioblastoma with IDH mutation is longer than that of patients with grade III anaplastic astrocytoma without IDH mutation. The prognostic impact of IDH1 mutations in diffuse astrocytoma remains controversial because at least one series with long follow-up reported a less benign postsurgical course of RT or chemotherapy were made, commonly for progressive disease. However, IDH1 status has not been shown to predict preferential benefit from a specific type of treatment, eg, RT versus chemotherapy.

In general, current analyses focus on the interrelations of various molecular markers—for instance, nearly all 1p/19q codeleted tumors also show IDH1/2 mutations among low-grade and anaplastic gliomas. In that regard, there is also speculation that the predictive value of MGMT status for benefit from alkylating agent chemotherapy may be restricted to patients with IDH wild-type tumors rather than being dependent on WHO grade. Altogether, current data suggest that IDH1/2 mutations can be used to distinguish a separate class or lineage of gliomas and that IDH1/2 status may become the cornerstone to separate various subtypes of glial tumors in the near future.

Outlook

Molecular markers have already shaped the design and conduct of several investigator-initiated and industry clinical trials in the field of gliomas, and information from such trials has been invaluable to demonstrate the potential impact of routine molecular testing. To date, a set of 3 molecular markers—1p/19q codeletion, MGMT promoter methylation, and IDH1/2 mutation—have gained importance in routine clinical decision making. The use of these markers will improve patient outcome and reduce cost and toxicity from ineffective treatments. More advances are to be expected: testing for the epidermal growth factor receptor (EGFR) vIII mutation may be implemented if randomized trials demonstrate activity of EGFR vIII–targeted vaccination; furthermore, pending demonstration of activity and approval, there will be an urgent need to define biomarkers allowing selection among the increasing repertoire of anti-angiogenic agents for glioblastoma. In contrast, the potentially more powerful high-throughput analyses, which have led to a reclassification, eg, of glioblastomas based on RNA expression profiles and DNA methylation patterns, have not yet had the awaited clinical impact because they have so far not allowed derivation of useful information for clinical decision making. Yet, we anticipate that such molecular signatures, possibly complemented by targeted sequencing of a panel of glioma-associated genes using next-generation sequencing technologies, will ultimately be made widely available and be increasingly used in neuro-oncology.

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