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REVIEW

Molecular markers in gliomas: impact for the clinician

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Abstract Over the last decade, understanding of glioma on a molecular level has greatly expanded. However, optimal incorporation of molecular markers into clinical care is controversial. We briefly review the potential utility of molecular stratification in refining histologic diagnosis, prognosis, and treatment decisions, focussing on 1p/19q co-deletion, *MGMT* promoter methylation, *EGFR* mutations, and *IDH* mutation. The most recently discovered *IDH* mutation is a striking example of a rapid implementation of a molecular marker for prognostication into common clinical use.

Keywords Glioma · MGMT · Molecular · 1p19q · Prognostic · Predictive · EGFR · IDH

Introduction

Adult patients with malignant gliomas almost always ultimately die from their disease. However, if the biology of gliomas is elucidated, targeted therapies may allow individualized patient care tailored to tumor biology. For example, the last several years have led to promising discoveries allowing molecular sub-classification of high-grade gliomas [1, 2] that can also supplement classic histology.

At this time, we rely primarily on clinical factors such as age, Karnofsky performance status, tumor size, presence of neurologic symptoms, and extent of resection to inform prognosis. These parameters and others have been used to identify prognostically important classes using recursive partitioning analysis (RPA) for patients with anaplastic astrocytomas and glioblastomas (GBMs) [3, 4]. They have been proven useful and were validated by subsequent glioma trials both at diagnosis and recurrence [4, 5]. They are critical stratification factors for randomized phase III clinical trials and for interpretation of single arm phase II studies to ensure valid historic controls are used although selection bias cannot be completely eliminated, as would a control arm in a randomized trial. However, molecular stratification is also emerging as key to ensure trials with multiple arms are adequately balanced, and that results of single arm studies are not misinterpreted.

Currently there is no molecular marker in neuro-oncology to accurately predict drug responsiveness of tumors as stringently as the oncogene *BCR-ABL* in chronic myelogenous leukemia. However, *MGMT* promoter methylation predicts enhanced sensitivity to temozolomide chemotherapy, and some data suggest that response to epidermal growth factor receptor (EGFR) inhibitors depends on mutations in *EGFR* [6, 7]. Advances in understanding glioma biology may, therefore, assist in histologic classification, prognostication, and treatment decisions.

In relation to these clinical issues, this review will focus on *MGMT* promoter methylation, 1p19q co-deletion, isocitrate dehydrogenase (*IDH) 1/2* mutation, and *EGFR* amplification/mutation (Table 1).

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Table 1 Frequency and possible role of tumor markers in glioma

Molecular marker	WHO II low grade	WHO III anaplastic	WHO IV glioblastoma	Diagnostic role	Prognostic in
MGMT promoter methylation	~93% [8]	~50–80% [13, 14]	~45% [9] ~40% 1°GBM ~70% 2°GBM		WHO II–IV [9–15, 18]
1p19q co-deletion	~85% [30]	~65% [30]	~5–25% [42–45]	WHO III oligodendroglial subtype [33–39]	WHO II–III [14, 40, 46–48] WHO IV unclear [18, 43, 45, 49]
IDH 1/2 mutation	~70–80 % [64, 65]	~65–70% [64–66]	<10% 1° GBM [64] >80% 2° GBM [64]	WHO I versus II [70]	WHO II–IV [14, 66, 71]
EGFR amplification/ mutation		~10% [78]	~45% [2]	WHO III astrocytic subtype [74, 75] EGFR vIII 1° GBM [73]	WHO IV unclear [18, 76–78]

MGMT promoter methylation

The importance of silencing DNA repair pathways, especially the DNA-repair enzyme AGT (O^6-alkylguanine DNA alkyltransferase) encoded by the gene *MGMT* (O^6-methylguanine-DNA-methyltransferase), has been the subject of substantial debate in recent years. A methylated (and thereby silenced) *MGMT* promoter is observed in many cancers, including low-grade gliomas (up to 93% in one series) [8], and in 45% in a series of GBMs [9].

The landmark European Organisation for Research and Treatment (EORTC)-National Cancer Institute of Canada (NCIC) study demonstrated a survival advantage from the addition of the DNA methylating agent temozolomide to radiotherapy [10]. A companion molecular study of archival pre-treatment tissue [9], and 5-year follow up data [11] also demonstrated that patients with *MGMT* methylated tumors derive the most benefit from temozolomide. For example, median survival was longer by 8.1 months in methylated cases (23.4 for radiotherapy and temozolomide versus 15.3 for radiotherapy alone); by contrast, there was less than 1-month difference in median survival in unmethylated cases (12.6 versus 11.8) [11]. However, it remains unclear whether a more favorable outcome in *MGMT* methylated cases results from enhanced sensitivity to alkylating agents or rather reflects a broader advantageous molecular profile of which *MGMT* methylation is one part.

The "broader view" is supported by the observations that methylated tumors also draw benefit from radiation therapy alone [9–14] or from non-alkylating drugs [15]. For example, survival following radiotherapy alone in the EORTC-NCIC study was 15.3 months in methylated cases versus 11.8 months in unmethylated cases. It is possible that temozolomide administered for disease progression after radiotherapy in temozolomide-naïve patients may explain these results, at least in part. However, they also suggest that our understanding of the mechanism by which *MGMT* promoter methylation affects outcome is incomplete at this time. In addition, MGMT protein expression (technically AGT but MGMT is now widely adopted as the nomenclature for both gene and protein product) [16] does not correlate with temozolomide efficacy [17, 18], probably because of contamination by normal tissue, but also suggesting a more complex mechanism than simply *MGMT* gene silencing by promoter methylation. Finally, patients with tumors that do not exhibit a methylated promoter also survive longer following treatment with temozolomide and radiotherapy than radiotherapy alone at diagnosis [11].

Therefore, it appears that *MGMT* methylation status is prognostic for survival regardless of therapy, and likely at least partially predictive of enhanced sensitivity to DNA alkylating chemotherapeutics. This has led some to advocate radiotherapy alone, without temozolomide, in patients with newly diagnosed GBM harboring unmethylated disease. It may be appropriate to modify therapy based on *MGMT* status in a clinical trial, such as restricting entry to those with or without *MGMT* methylated tumor [15] as in the CENTRIC study (EORTC 26071-22072, NCT00689221). However, it should be noted that the current standard of care outside of a trial is radiotherapy and temozolomide regardless of *MGMT* status.

In the unmethylated setting, whether prolonged exposure to alkylating agents might deplete MGMT and thereby overcome MGMT mediated DNA repair mechanisms is an area of active investigation. Various alternative temozolomide dosing schedules are under investigation [19] some of which appear promising in early trials for newly diagnosed [20] and recurrent GBM [21–23]. These may prove superior to standard dosing, especially in cases without *MGMT* methylation, inferior, or equivalent with more or

less toxicity. However, MGMT is not the only DNA repair mechanism of importance in gliomas. Accordingly, it is notable that the British Medical Research Council (MRC) trial BR12 of chemo-naïve patients with recurrent high-grade gliomas did not demonstrate superior efficacy with dose-intense temozolomide (100 mg/m^2, 21/28) versus standard dosing (200 mg/m^2, 5/28) [24]. In fact, unexpectedly, progression-free survival favored standard dosing (p= 0.023), and there was a trend toward favoring survival [24] (Michael Brada, personal communication). Radiation Therapy Oncology Group (RTOG) trial 0525 is a phase III study that randomized patients with newly diagnosed GBM to initiate either standard or dose-intense temozolomide after radiotherapy. Accrual is complete and results are pending. Another randomized trial dealing with a similar issue in recurrent GBMs is still accruing patients (DIRECTOR trial, conducted by the Neurooncology Working Group (NOA) of the German Cancer Society).

Elsewhere in this issue, Riemenschneider et al. [25] discuss analysis of and controversies surrounding *MGMT* methylation in more detail.

1p19q co-deletion

Approximately 5–10% of all primary brain tumors are oligodendrogliomas [26]. Loss of genetic material on the short (p) arm of chromosome 1 and the long (q) arm of chromosome 19, so-called chromosome 1p19q co-deletion, was first reported as an observation in oligodendroglial tumors in 1994 [27]. Cairncross et al. then reported chemosensitivity in patients with anaplastic oligodendrogliomas harboring deletion of 1p and particularly co-deletion of 1p and 19q [28]. Further study ensured, and it is now known that chromosomal loss results from an unbalanced translocation [29]. Nearly 85% of low-grade oligodendrogliomas and 65% of anaplastic oligodendrogliomas harbor 1p19q co-deletion [30]. The higher frequency in lower grade tumors suggests deletion is an early event in tumor formation (J. Gregory Cairncross, personal communication). Indeed, observational studies suggest that co-deletion may be more common in cases of anaplastic oligodendroglial tumors with a prior history of low-grade glioma [31].

1p19q deletion status is frequently used to refine histologic diagnoses. The current World Health Organization (WHO) classification of gliomas is based on histopathology which divides gliomas into astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas as the most common subtypes [32]. However, histopathology alone does not identify molecular subtypes. For example, there is high inter-observer variation in diagnosing oligodendrogliomas [33], and expert panels often disagree [34–38]. As 1p19q co-deletion is most common in oligodendrogliomas, it is often used in the community and at academic centers to support a diagnosis of oligodendroglioma in cases with ambiguous histology [39]. However, molecular analysis alone is insufficient for diagnosis, and should be used to complement rather than replace classic histopathology [34, 36, 39, 40]. Approximately 20% [41] of otherwise WHO grade IV tumors (GBMs) contain oligodendroglial features (termed GBM-O according to the most recent 2007 WHO classification) [32]. GBM-O likely harbors a higher frequency of 1p and /or 19q deletion than purely astrocytic GBM, but the reported frequencies vary from approximately 5% [42, 43] to approximately 25% [44, 45].

1p19q co-deletion is prognostic in anaplastic gliomas, validated in three randomized trials [14, 46, 47]. As a consequence, the two open phase III trials for anaplastic gliomas use both histology and deletion status as eligibility criteria. EORTC 26053-22054 (Concurrent and Adjuvant Temozolomide Chemotherapy for patients with NON-1p19q deleted anaplastic glioma [CATNON] intergroup study) randomizes patients without 1p19q co-deleted anaplastic gliomas to radiotherapy with or without concurrent and/or adjuvant temozolomide. NCCTG N057 (for 1p19q co-deleted tumors, also called CODEL) will randomize patients with 1p19q co-deleted anaplastic gliomas to radiotherapy, radiotherapy with concurrent and adjuvant temozolomide, or temozolomide. 1p19q co-deletion is likely also prognostic for low-grade gliomas, but the data are less well defined. One study suggested that chromosome 1p status is a significant prognostic marker in low-grade gliomas regardless of histologic subtype [48]. A recently completed randomized trial of the EORTC 22033-26033/NCIC in patients with WHO grade II gliomas stratified tumors by 1p status and will provide more information. There is inconsistency regarding the prognostic value of 1p and 19q deletion in GBMs with oligodendroglial features. For example, one study suggests that long-term survivors from GBM do not commonly harbor 1p19q co-deletion [49]. However, 1p and 19q co-deletion is uncommon in GBMs as is long-term survival, making it difficult to address this issue definitively with sufficiently powered studies when clinical prognostic factors (e.g., age, extent of resection) are also considered [43, 45]. The variability observed in both deletion frequency and prognostic importance across studies may be explained at least in part by the histologic overlap between GBM-O and anaplastic oligodendroglioma, causing inclusion criteria inconsistencies. Finally, the prognostic significance of 19q deletion without 1p deletion, 1p deletion without 19q deletion, and 1p19q co-deletion with other chromosomal abnormalities (such as 10q deletion or chromosome 7 gain) is not definitively understood with the existing data.

Although 1p19q co-deletion is clearly correlated with longer survival, it remains debated whether 1p19q status should alter therapy. Of note, the favorable prognosis associated with 1p19q co-deletion in oligodendroglial tumors may be reduced if no post-operative therapy is administered. In one study, after surgery alone, combined 1p19q co-deletion was not prognostic for progression-free survival using multivariate analysis in a small number of patients with WHO grade II and III tumors [50]. This observation suggests that the mechanism by which 1p19q co-deletion contributes to tumor biology may be through reduced expression of chemotherapy and/or radiotherapy resistance factors. Therefore, 1p19q co-deletion may improve outcome only if surgery is followed by further therapy. However, others have reported opposing results [51], and selection bias is a potential confounder. Moreover, almost no neuro-oncologists would advocate observation for anaplastic oligodendroglial tumors regardless of 1p19q status [52].

Regarding definitive therapy, the standard therapy for all WHO grade III–IV tumors, including anaplastic oligodendrogliomas, before the discovery of 1p19q co-deletion was radiotherapy alone. This resulted from early multicenter studies conducted in the 1970s comparing radiotherapy with or without chemotherapy against chemotherapy alone or supportive care only [53, 54]. These studies addressed whether radiotherapy improves survival in high-grade gliomas, as that was debated at the time. Although radiotherapy was clearly demonstrated as beneficial, these early studies did not distinguish among various high-grade glioma histologies and almost all patients enrolled had astrocytomas [55]. However, by the late 1980s and early 1990s reports emerged of exquisite chemosensitivity among both recurrent [56, 57] and newly diagnosed oligodendrogliomas [57, 58], especially those harboring 1p19q co-deletion [59]. Therefore, EORTC 26951 [47] and RTOG 9402 [46] were conceived as phase III randomized trials to evaluate the efficacy of adding chemotherapy (using procarbazine, lomustine, and vincristine collectively called PCV) to radiotherapy in comparison to radiotherapy alone (then the standard). Both trials demonstrated, somewhat surprisingly, that overall survival was not prolonged by incorporating PCV into the up-front regimen, either immediately before [46] or after [47] radiotherapy. However, both trials also collected tissue used for 1p19q analysis, and both demonstrated prolonged progression-free survival following combined therapy in 1p19q co-deleted cases. The toxicity of PCV is substantial, and the intensified PCV regimen in RTOG 9402 (shorter cycles with higher doses of each agent) resulted in one fatal toxicity [46]. Accordingly, without a survival advantage, it is unclear whether the benefit of a longer progression-free interval outweighs the risks of potential toxicity. Of note, however, the median survival in the 1p19q co-deleted cohort was not reached for patients treated with radiotherapy and intensive-PCV in RTOG 9402 as the survival curves began to separate [46], and further maturity of the data may well demonstrate a survival advantage on the experimental arm [60]. Longer follow up has not been conducted yet for EORTC 26951 (Martin J. van den Bent, personal communication).

Finally, the median survival of patients with anaplastic oligodendrogliomas is approximately 5 years [26], and longer for those harboring 1p19q co-deletion. This is superior to the prognosis for astrocytomas of the same histologic grade [26]. Therefore, there is a small but real risk of delayed neuro-cognitive decline associated with early radiotherapy for anaplastic oligodendrogliomas, similar to that observed in long-term survivors of low-grade gliomas [61] or brain metastases [62]. This leads many neuro-oncologists, up to 42% in one survey, to advocate chemotherapy alone for newly diagnosed anaplastic oligodendrogliomas harboring 1p19q deletion [52]. A retrospective study suggests deferring radiotherapy until first or later progression is reasonable in such patients [31]. A phase III prospective study by the Neurooncology Working Group (NOA) of the German Cancer Society (NOA-04) also suggests that initial chemotherapy is not inferior to radiotherapy in anaplastic gliomas [14] although the study design has been questioned [63]. The CODEL study will incorporate quality of life/neuro-cognitive endpoints to address some of these issues.

IDH 1/2 mutation

Sequencing of the genome recently identified mutations in the isocitrate dehydrogenase 1 and 2 gene (*IDH 1/2*) that occur in the majority of WHO grade II–III gliomas and secondary GBMs [64, 65], all of which harbor a better prognosis compared to wild type cases [66]. A high frequency in low-grade gliomas and secondary GBMs suggests a role in early tumor development [64] similar to 1p19q co-deletion in oligodendrogliomas. Therefore, it is not surprising that all 1p19q-deleted tumors apparently also harbor *IDH1* or *IDH2* mutations [67]. *IDH* appears to function as a tumor suppressor when inactivated through mutation [68], which causes the IDH enzyme to lose its ability to catalyze conversion of isocitrate to alpha-ketoglutarate and induces HIF1-alpha (hypoxia-inducible factor), which triggers the angiogenic process. However, the precise mechanism of its effect on tumor biology is currently unclear [68, 69].

IDH mutations occur in WHO grade II–IV tumors, and are not currently used to supplement classic histology. Yet, pilocytic astrocytomas (WHO grade I) that are potentially

curable by complete resection, rarely harbor *IDH* mutations. Occasionally they are difficult to distinguish histologically from diffuse infiltrating WHO grade II astrocytomas (with almost no curative potential). BRAF abnormalities that occur in 60–80% of pilocytic astrocytomas and almost never in diffuse astrocytomas seem to be helpful in this regard [70].

More importantly, the value of *IDH 1/2* mutations relates to prognosis, as demonstrated in the German NOA 04 trial where patients with WHO grade III gliomas received primary radiotherapy or primary chemotherapy followed by cross-over at progression [14] and EORTC 26951 in which patients with anaplastic oligodendroglial tumors received primary radiotherapy alone or combined with PCV [71]. Both studies demonstrated longer survival correlated with *IDH* mutation. A French series also demonstrated that *IDH1* mutations independently predicted longer survival for patients with both low- and high-grade gliomas [66]. Others reported analogous prognostic value across glioma grades [64], and also observed that 100% of 1p19q deleted tumors harbor mutations in *IDH1* or *IDH2* [72].

At this time, IDH mutations do not appear predictive for outcome to a specific therapy. However, our understanding of the interplay between *IDH* mutation and oncogenesis is currently limited.

EGFR mutation

EGFR was among the first cell-surface glycoproteins recognized as amplified and re-arranged in GBM and acting as an oncogene. Many GBMs exhibiting *EGFR* amplification have *EGFR* mutations, most commonly the variant 3 (EGFRvIII) (approximately 40%), which is truly tumor-specific and results from deletion of exons 2–7 leading to constitutive receptor activity [73].

EGFR amplification and mutation define a distinct subset of tumors. *EGFR* abnormalities are typically associated with GBM and anaplastic astrocytoma rather than oligodendrogliomas [74, 75]. This observation may help to refine histologic diagnosis in ambiguous cases.

The prognostic relevance of *EGFR* amplification and *EGFRvIII* mutation in GBM remain controversial. Tumors expressing *EGFRvIII* behaved more aggressively in one study, but only when other prognostic factors were considered [76]. In a population-based study, the presence of *EGFR* amplification did not significantly affect survival of patients with GBM at any age [77]. The prognostic importance of EGFR abnormalities is inconclusive at this time, with conflicting data as reviewed elsewhere [77, 78].

Similarly, whether therapy should be tailored based on presence or absence of *EGFR* amplification or mutation is an area of active study. Available data is insufficient to guide management decisions outside of a clinical trial. EGFRvIII-expressing tumor cells are an ideal target for passive and active immunotherapy as the mutation does not occur in normal glia. Trials with various vaccination approaches are underway with promising early results [79], but selection bias (i.e., exclusion of patients with less than gross-total resection) and accrual are challenges to interpretation and study completion.

EGFR tyrosine kinase inhibitors (TKIs) have been studied in multiple trials, typically for recurrent GBM with almost universally negative results [80–85]. Poor efficacy may result from inadequate drug penetration into brain tumor tissue of erlotinib at standard dosing [86, 87]. Gefitinib may have superior penetration [86, 88] but is unavailable in the United States. Lapatinib also may become sequestered in brain tumor tissue [89], but has been studied in gliomas less extensively than other EGFR TKIs.

It is controversial whether EGFR amplification or mutation predicts sensitivity to EGFR TKIs, presuming adequate drug delivery. One retrospective analysis of pretreatment tissue from patients prospectively enrolled in multicenter phase I/II studies demonstrated that *EGFRvIII* mutation in the setting of retained expression of its downstream mediator, phosphatase and tensin homolog on chromosome ten (PTEN), strongly predicted radiographic response of recurrent malignant gliomas to erlotinib and gefitinib [6]. Another study similarly demonstrated *EGFR* overexpression/amplification and reduced AKT activity (which results from PTEN retention) were predictive of erlotinib response [90]. A case report also suggests that this molecular signature is predictive of response [91]. However, others have questioned these results [92]. For example, a prospective trial (EORTC 26034) did not find EGFRvIII or PTEN to correlate with clinical benefit [93]. The discrepancy in findings may result from lack of uniformity in defining both clinical efficacy (e.g., 6-month progression-free survival versus response rate as well as differing criteria for designation of radiographic response) and scoring of EGFR/PTEN anomalies in human tumor samples. In addition, all of these studies used a similar design—to enroll patients without regard to molecular information and then retrospectively correlate EGFR and PTEN anomalies with clinical outcome. The frequency of EGFRvIII and PTEN co-expression is so low (approximately 5–10% of cases in our experience) that a prospective trial exclusively for patients harboring tumors with such a molecular profile is impractical. Moreover, neither *EGFR* amplification, nor *EGFRvIII* mutational analysis, nor PTEN analysis is routinely available at most centers. A planned prospective study of EGFR tyrosine kinase inhibition will require the presence of *EGFRvIII* mutation for eligibility

and use a different erlotinib dosing schedule than previously administered [87] for gliomas to potentially overcome resistance mediated by *PTEN* loss.

Conclusions

Diagnostic and prognostic markers are increasingly implemented in neuro-oncology as decision-making tools toward more objective classification of gliomas, to prognosticate, and to guide therapy. 1p19q co-deletion supplements classic histology to clarify a diagnosis of oligodendroglioma. By contrast, EGFR abnormalities are most common in astrocytomas. The prognostic value of various markers is well established, although their predictive value in guiding specific therapy is an area of active research. For example, *MGMT* promoter methylation, 1p19q co-deletion, and *IDH* 1/2- mutation each indicate a more favorable disease outcome independent of the type of therapy. This holds true for WHO grade II–IV gliomas, except perhaps for an unclear significance of 1p19q co-deletion in GBMs. In clinical trials, accrual must be stratified accordingly in order to avoid biasing results.

Linkage of "favourable prognosis" markers, or a "hierarchy", is still not well understood. However, 1p19q co-deletion seems to occur exclusively of EGFR abnormalities [75] but co-segregates with *IDH* mutation [67]. Moreover, in oligodendroglial tumours there is a strong correlation between the presence of *MGMT* promoter methylation, 1p19q co-deletion, and *IDH 1/2* mutation, at least in anaplastic disease [13, 14, 71, 72]. Data in GBMs are less clear [18]. Whether the underlying mechanisms act independently or together remains to be investigated.

It is tempting to speculate that patients with tumors that harbor poor prognostic molecular markers (e.g., unmethylated *MGMT* promoter, wild type IDH1 and IDH2, lack of 1p19q deletion) should be treated more intensely. One example is incorporation of bevacizumab, approved for treatment of recurrent GBM in the United States and Switzerland, into the treatment administered at diagnosis, although benefit at recurrence is still debated [94]. Ongoing GBM trials (RTOG 0825, AVAGLIO) will address this issue. However, more is not necessarily better, and it is unclear whether more aggressive therapy improves survival for such patients or only risks additional toxicity [95]. For example, in anaplastic oligodendroglial tumors without 1p19q co-deletion, there was neither a progression-free survival nor overall survival benefit for radiotherapy and PCV versus radiotherapy alone in one randomized phase III trial (RTOG 9402) [46].

Therefore, to date there is no validated predictive biomarker to accurately guide a clinician in deciding treatment in routine practice. However, this remains an area of active investigation and multiple clinical trials are incorporating molecular information into their design, either as stratification factors to balance treatment arms in randomized studies, or as eligibility criteria.

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