

Recent developments in predictive biomarkers of pediatric glioma (Review)

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Abstract. The presence of certain cancer-related genetic and epigenetic alterations in the tumor affects patient response to specific cancer therapies. The accurate screening of these predictive biomarkers in molecular diagnostics is important since it enables the tailoring of optimal treatment based on molecular characteristics of the tumor. We searched the electronic database PubMed for preclinical as well as clinical controlled trials reporting on various multiple predictors of glioma. It was observed clearly that multiple approaches are evolving and a few of them have also shown promising results. Depending on the type of gene alteration, a wide variety of methods may be applied in biomarker testing. Among the novel methods is next-generation sequencing (NGS) technology, enabling simultaneous detection of multiple alterations. The aim of this review is to discuss the predictive or potentially predictive genetic and epigenetic alterations of diffuse gliomas. The review concludes that NGS technology is the future and may likely replace, at least to some extent, the current routinely used methods, including FISH, IHC, and PCR-based methods, in clinical diagnostics.

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1. Introduction

Tumors in the brain and central nervous system were estimated to account for 1.8% (256,000) of new cancer cases and 2.1% (142,000) of cancer deaths worldwide in 2012 (1,2). This review focuses on gliomas, which arise from the supportive glial cells of the brain and account for approximately 30% of all central nervous system and brain tumors and 80% of malignant brain tumors (3). In addition to heritable risk variants, other factors with a proposed link to gliomas include, for example, ionizing radiation associated with increased risk and allergic conditions associated with reduced risk of gliomas (4). Additionally, some monogenic Mendelian syndromes, such as neurofibromatosis 1, Li-Fraumeni syndrome, tuberous sclerosis, and Lynch syndrome, predispose to gliomagenesis, but only a small proportion of all glioma cases is explained by these syndromes.

2. Histopathology and grading of gliomas

Based on cellular morphology, the World Health Organization (WHO) classification divides gliomas into three major subtypes: astrocytomas, oligodendrogliomas, and a mixture of these two cell types, oligoastrocytomas (5). Both oligodendrogliomas and oligoastrocytomas are also known as oligodendroglial tumors. The histological WHO grading system provides information on the biological aspects of the tumors, aiding prognosis and prediction of treatment response. WHO grade I tumors are benign, discrete, and curable by surgical removal, whereas WHO grade II-IV diffuse gliomas infiltrate into the surrounding brain tissue, thus preventing complete surgical removal and cure (6). Grade II tumors show increased cellularity, grade III tumors also show increased anaplasia and mitotic figures, and grade IV tumors show vascular proliferation and necrosis in addition to the aforementioned features. Grade IV astrocytoma, glioblastoma, is the most frequently occurring and most malignant glioma subtype. It is further subdivided into primary glioblastomas (95% of cases), arising without evidence of pre-existing lower grade gliomas, and secondary glioblastomas (5% of cases), developing from lower grade gliomas (7). Primary and secondary glioblastomas can not be distinguished by histopathology, but they exhibit genetic and epigenetic differences, and patients with secondary glioblastomas are typically younger at diagnosis (8). Certain molecular alterations are frequently seen in

specific glioma subtypes and grades, and thus, they may further aid in the classification of tumors. Example of these alterations include codeletion of 1p/19q in oligodendroglial tumors (9), *IDH1* mutation in diffuse grade II-III gliomas and secondary glioblastomas (10), and loss of heterozygosity (LOH) of chromosome 10q, *EGFR* amplification, *TP53* mutations, p16^{INK4a} (*CDKN2A*) deletions, and *PTEN* mutations in glioblastomas (7). In addition to contributing to the pathogenesis of gliomas, many of these molecular alterations have prognostic significance for prediction of the outcome of patients (11). For example, codeletion of 1p/19q and *IDH1* mutations have been associated with favorable prognosis, whereas LOH 10q and *PTEN* mutations have been linked to poor prognosis.

Many factors, such as WHO grade, tumor location, age of the patient, performance status, and presence of specific molecular alterations, contribute to the outcome and treatment response of glioma patients. Population-based studies have shown the following 5-year survival rates (mean of the studies) for different glioma subtypes and grades: 68.5% in oligodendrogliomas (grade II), 50% in oligoastrocytomas, 41.9% in astrocytomas (grade II), 34.4% in anaplastic oligodendrogliomas (grade III), 19.8% in anaplastic astrocytomas (grade III), and 3.4% in glioblastomas (grade IV) [reviewed by Ostrom *et al.*, 2014 (4)]. Despite the relatively good survival from slowly growing low-grade gliomas, they eventually progress to higher-grade gliomas (12).

3. Predictive biomarkers in adult diffuse gliomas

Codeletion of chromosomes 1p and 19q. Combined loss of whole chromosome arms 1p and 19q, potentially caused by an unbalanced translocation between the arms early in tumorigenesis (13), is a frequent change in oligodendroglial tumors, reported in 44-89% of oligodendrogliomas (9) and in 19-38% of oligoastrocytomas (14). In astrocytomas/glioblastomas, the codeletion of 1p/19q is a rare event. Although the tumor suppressor genes involved in the 1p/19q loss have not been unequivocally identified, some candidate genes have been discovered within the lost chromosome arms, including genes coding for capicua transcriptional repressor (CIC) located at 19q13.2 and far upstream element (FUSE)-binding protein 1 (FUBP1) located at 1p31.1 (15). In patients diagnosed with anaplastic oligodendroglial tumors, the codeletion of 1p/19q has been associated with better survival when the patients are treated with radiotherapy and combination chemotherapy of alkylating agents procarbazine and lomustine (CCNU) together with microtubule inhibitor vincristine (PCV) compared with radiotherapy alone (16). The predictive significance of codeleted 1p/19q has also been indicated in low-grade gliomas, which show a good response to temozolomide chemotherapy (17). In addition to the predictive value of combined 1p/19q loss, it also serves as a prognostic biomarker of a favorable prognosis (18).

O⁶-methylguanine-DNA methyltransferase (MGMT) promoter hypermethylation. MGMT is a DNA repair enzyme that functions in the removal of alkyl groups from O⁶ position of guanine caused by DNA-alkylating agents such as temozolomide. Hypermethylation of the promoter region of the *MGMT* gene located at 10q26 leads to reduced

MGMT expression and DNA repair activity, affecting the sensitivity of *MGMT*-methylated gliomas to alkylating agents (19). *MGMT* hypermethylation has been associated with improved survival in glioblastomas treated with combined temozolomide and radiotherapy compared with radiotherapy alone (20). In a study by Hegi *et al.* (21), the median OS was 21.7 months (95% CI, 17.4-20.4 months) for *MGMT*-methylated glioblastoma patients treated with temozolomide plus radiotherapy compared with 15.3 months for patients treated with radiotherapy (p=0.007). For patients with unmethylated *MGMT*, the median OS was very similar regardless of the treatment received. Furthermore, among *MGMT*-methylated glioblastoma patients, the median progression-free survival (PFS) was 10.3 months (6.5-14.0) for temozolomide plus radiotherapy and 5.9 months (5.3-7.7) for radiotherapy alone (p=0.001), and among patients with unmethylated *MGMT*, 5.3 months (5.0-7.6) for temozolomide plus radiotherapy and 4.4 months (3.1-6.0) for radiotherapy alone (p=0.02). Recently, temozolomide treatment was compared with radiotherapy in elderly (>65-70 years) glioblastoma patients with and without *MGMT* hypermethylation (22). These studies suggested that *MGMT* hypermethylation predicts a favorable response to temozolomide treatment in elderly glioblastoma patients, whereas unmethylated *MGMT* seemed to predict lack of survival benefit from alkylating agent chemotherapy. For example, Wick *et al.* (22) showed that the glioblastoma patients with *MGMT* hypermethylation had longer event-free survival when treated with temozolomide than patients treated with radiotherapy. On the other hand, the patients with unmethylated *MGMT* who received temozolomide showed shorter survival than those who underwent radiotherapy. Resistance to temozolomide often emerges also in patients with hypermethylated *MGMT* promoter and a good primary response to temozolomide. Although the underlying mechanism for this resistance is not yet established, increased *MGMT* activity and DNA mismatch repair deficiency have been suggested (23).

Hypermethylation of the *MGMT* promoter has been reported to occur in approximately 50% of astrocytomas (including glioblastomas) and in approximately 70% of oligodendroglial tumors (24). Studies in recent past have shown the value of *MGMT* hypermethylation in the prediction of favorable prognosis in various glioma subtypes (25,26). The *MGMT* methylation status has also been suggested to be useful in distinguishing pseudoprogression from real progression of cancer, as *MGMT* hypermethylation is significantly associated with pseudoprogression (27). Moreover, the presence of *MGMT* hypermethylation is significantly associated with *IDH1* mutation and 1p/19q codeletion (28). Interestingly, a recent report showed that the assessment of both *MGMT* methylation and *IDH1* mutation status in glioblastoma patients provides a better prediction of survival than either status alone (29). The longest survival was observed in patients carrying *MGMT* methylation and *IDH1* mutation, whereas patients with unmethylated *MGMT* and unmutated *IDH1* had the shortest survival. Furthermore, *IDH1* mutation status is suggested to affect how *MGMT*-methylated high-grade gliomas benefit from alkylating agent chemotherapy, since *MGMT* hypermethylation is associated with

a better survival in *IDH1*-negative but not *IDH1*-positive patients treated with chemotherapy (30).

***IDH1* mutations.** *IDH1* gene located at chromosome 2q33.3 codes for cytosolic isocitrate dehydrogenase 1 (NADP⁺) enzyme involved in the citric acid cycle. *IDH1* mutations are early alterations in gliomagenesis, suggested to occur before *TP53* mutations and codeletion of 1p/19q (31). The mutations in *IDH1* are detected in 64-100% of diffuse grade II-III gliomas, and secondary glioblastomas, but only in 5-7% of primary glioblastomas (32). The majority of mutations in *IDH1* affect the arginine amino acid at codon 132, which is substituted with histidine (R132H) in the most common type of mutations. Mutations in *IDH2* gene (at 15q26.1) encoding the mitochondrial isocitrate dehydrogenase 2 (NADP⁺) enzyme are also observed in gliomas, but at a lower frequency (approximately 3%) (32). *IDH1* and 2 enzymes catalyze the conversion of isocitrate to α -ketoglutarate, but when mutated, they begin to produce the oncometabolite 2-hydroxyglutarate, the accumulation of which is suggested to eventually lead to cancer-promoting alterations such as genome-wide histone and DNA methylation changes (33,34). The predictive value of *IDH1/2* mutations remains to be clarified; some studies have reported no impact of *IDH1* mutations on response to temozolomide in low-grade astrocytomas (35) or PCV chemotherapy in anaplastic oligodendrogliomas (26), whereas others have shown an improved response to temozolomide chemotherapy in *IDH*-mutant low-grade gliomas (36) and secondary glioblastomas (37) or a benefit from PCV chemotherapy in anaplastic oligodendroglial tumors (38). Recently, promising results have been obtained by a selective R132H-*IDH1* inhibitor, which appears to impair growth and promote differentiation of glioma cells harboring the *IDH1* mutation (39). *IDH*-mutated gliomas have been associated with a favorable prognosis in numerous studies (40).

4. Other potential therapeutic molecular targets in gliomas

Several clinical studies of novel therapeutic agents targeting single or multiple molecular alterations of gliomas have been performed in recent years and many studies are ongoing (41). Examples of investigated therapeutic molecular targets include cell surface molecular receptors and their ligands, such as EGFR, VEGF, VEGFR, PDGFR, and integrins, downstream signaling effectors, such as Ras, MAPK (ERK), mTOR, and protein kinase C, and other molecular targets, such as histone deacetylases and proteasome. Many of these molecular targets show increased expression or activation in gliomas. Despite the large number of studies performed on potential therapeutic agents (e.g., inhibitors), none has shown significant improvement in the survival of glioma patients.

5. Treatment of gliomas

The standard treatment options for newly diagnosed gliomas include surgical resection (or a biopsy if surgery cannot be performed), radiotherapy, and chemotherapy. Treatment for low-grade (grade II) diffuse gliomas consists of a resection, possibly followed by radiotherapy or chemotherapy (42).

Options for treatment of anaplastic (grade III) gliomas include surgical resection, followed by radiotherapy and/or chemotherapy, whereas standard care for patients (<65-70 years) with glioblastomas (grade IV) combines resection, radiotherapy, and chemotherapy with the alkylating agent temozolomide (43). Anaplastic oligodendroglial tumors harboring 1p/19q codeletion and elderly (>65-70 years) patients with glioblastomas harboring *MGMT* promoter hypermethylation can be treated by surgery and chemotherapy with or without radiotherapy (43). The blood-brain barrier complicates the treatment of gliomas since many chemotherapeutic drugs cannot be delivered to the central nervous system across the barrier, and even with a successful delivery, the concentration of the drug in the brain might be low (44).

6. Conclusions

It is concluded that next-generation sequencing (NGS) technology is the future and is likely to replace, at least to some extent, the current routinely used methods, including FISH, IHC, and PCR-based methods, in clinical diagnostics. The great benefit of targeted NGS over the other available methods is the possibility to simultaneously screen all known predictive biomarkers. NGS also has applications for analysis of methylation and gene expression. Collectively, NGS enables the assessment of a more complete picture of the molecular architecture of tumors, which could lead to more efficient treatment decisions.

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