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Current therapeutic approaches to diffuse grade II and III gliomas

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Abstract: The 2016 WHO classification of Tumors of the Central Nervous System brought major conceptual and practical changes in the classification of diffuse gliomas, by combining molecular features and histology into 'integrated' diagnoses. In diffuse gliomas, molecular profiling has thus become essential for nosological purposes, as well as to plan adequate treatment strategies and identify patients susceptible of target therapy. WHO grade II (low grade) and grade III (anaplastic) diffuse gliomas form a heterogeneous group of neoplasms, also known as 'lower-grade gliomas', characterized by a wide range of malignant potential. Molecular profile accounts for this biological diversity, and provides an accurate prognostic stratification of tumors in this group. Treatment strategies in lower-grade gliomas are ultimately based on molecular profile and WHO grade, as well as on patient characteristics such as age and Karnofsky performance status. The purpose of this review is to summarize recent advances in the classification of grade II and III gliomas, synthesize current treatment schemes according to molecular profile and describe ongoing research and future perspectives for the use of target therapies.

Keywords: anaplastic gliomas, diffuse low-grade gliomas, molecular biomarkers/WHO 2016 diagnostic criteria, targeted therapy

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Introduction

Diffuse gliomas are the most frequent primary brain tumors, and are graded II to IV, with grade IV or glioblastoma being the most frequent and the most aggressive. The term 'lower-grade gliomas' was created to designate WHO grade II and III astrocytomas and oligodendrogliomas, as opposed to glioblastoma. Although these tumors altogether account for only a minority of diffuse gliomas (30–35%),[1,2] they represent an important cause of morbidity and mortality in young adults, the population primarily affected by these neoplasms.

Lower-grade gliomas form a biologically heterogeneous group of tumors. Histology alone is often insufficient to make accurate prognostic estimates, and tumors belonging to the same WHO grade may display different malignant behavior, depending on their molecular profile.

In this review, we report the recent advances on oncogenesis and molecular classification of grade II and III gliomas. We discuss the prognostic factors and the current guidelines for treatment in light of the recent randomized trials, as well as the still unsolved and more controversial issues.

The molecular classification of diffuse grade II and III gliomas

The association of molecular markers to histology has recently allowed improvements in the diagnostic and prognostic stratification of lower-grade gliomas, and represents the cornerstone of the 2016 WHO classification of Tumors of the Central Nervous System.[3] Two molecular markers are essential for nosological purposes in this classification: the isocitrate dehydrogenase (IDH) mutation and the chromosome 1p/19q codeletion.[3] Based on the presence of these two genetic alterations, lower-grade gliomas can be divided

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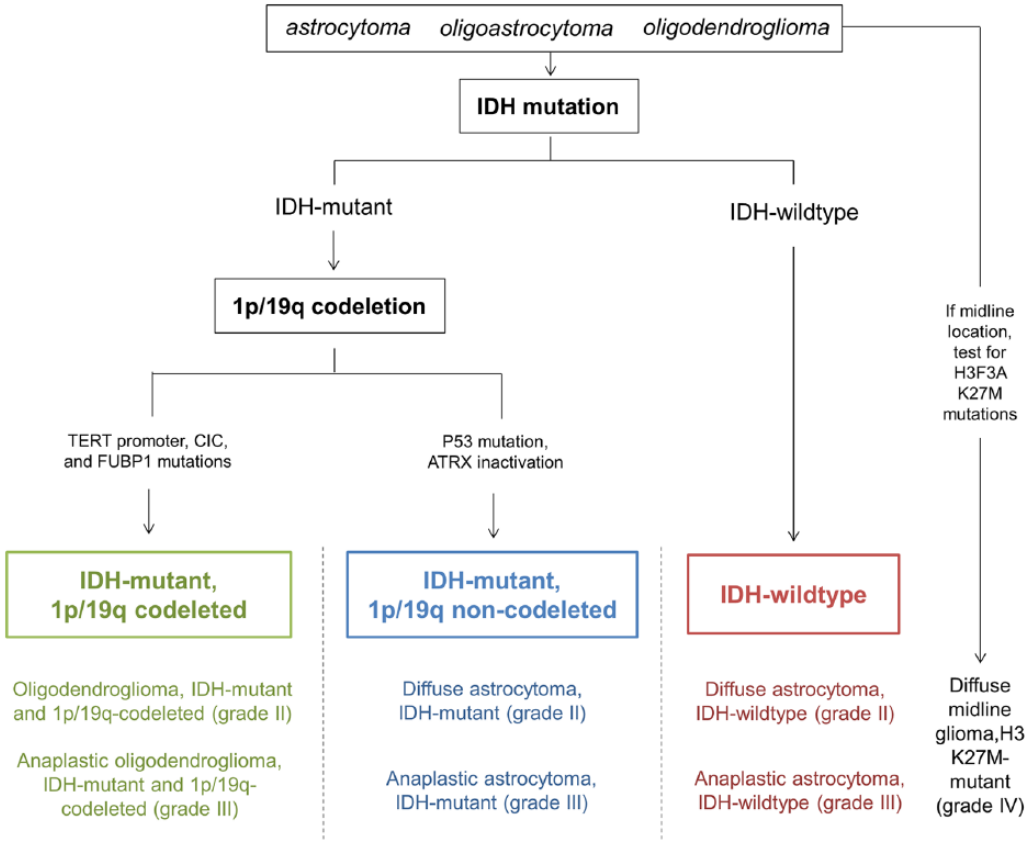

Figure 1. A simplified diagnostic algorithm for the integrated diagnosis of lower-grade gliomas according to the 2016 WHO classification. Besides the IDH mutation and the chromosome 1p/19q codeletion, diffuse gliomas located along the midline should be tested also for the H3 K27M mutation. The presence of this molecular marker identifies in fact a distinct nosological entity ('diffuse midline glioma, H3 K27M-mutant') assigned WHO grade IV.

into three distinct molecular subgroups, since 1p19q codeletion is systematically associated with IDH mutation, corresponding to separate biological entities: (1) IDH-mutant, 1p/19q codeleted; (2) IDH-mutant, 1p/19q non-codeleted; and (3) IDH-wildtype gliomas.[4,5] Final diagnosis ultimately results from molecular subgroup and WHO grade (Figure 1).

The main characteristics of the three molecular subgroups identified by the IDH mutation and the 1p/19q codeletion are detailed hereafter.

(1) **Oligodendrogliomas (WHO grade II) and anaplastic oligodendrogliomas (WHO grade III), IDH-mutant and 1p/19q codeleted.** These tumors usually show an oligodendroglioma phenotype on hematoxylin–eosin sections and display INA (internexin alpha) expression on immunohistochemistry.[6] Molecular alterations frequently detected in this group are TERT promoter (>90%),[4,7] CIC (35–80%)[4,8–10] and FUBP1 (15–30%)[4,9,10] mutations. TERT promoter mutation is helpful to support diagnosis when the results for 1p/19q codeletion are ambiguous.

(2) **Diffuse astrocytomas (WHO grade II) and anaplastic astrocytomas (WHO grade III), IDH-mutant.** These tumors generally show an astrocytoma or oligoastrocytoma morphology on hematoxylin–eosin sections and display p53 overexpression and/or ATRX loss on immunohistochemistry. Consistently, mutations in the TP53 gene and/or inactivating alterations in the ATRX gene are detected in the vast majority of cases.[4,11,12]

(3) **Diffuse astrocytomas (WHO grade II) and anaplastic astrocytomas (WHO grade III), IDH-wildtype.** These tumors usually do not display INA or p53

Table 1. Median overall survival in lower-grade gliomas according to molecular subgroup and WHO grading.

Molecular subgroup	IDH-mutant, 1p/19q codeleted		IDH-mutant, 1p/19q non-codeleted		IDH-wildtype		Reference
WHO grade	**II**	**III**	**II**	**III**	**II**	**III**	
Median overall survival (years)	12.6	11.6	7.3	4.9	5	1.7	Labussière and colleagues[5]
	nr	nr	≈ 9	≈ 6	nd	≈ 2	Suzuki and colleagues[16]
	⩾ 12	≈ 11	≈ 8	≈ 5	nd	≈ 2	Chan and colleagues[17]

nd, not determined; nr, not reached.

expression on immunohistochemistry nor ATRX loss. These tumors have been named 'triple negative' gliomas,[13] as they lack IDH mutations, p53 mutations and the chromosome 1p/19q codeletion. Tumors in this group may harbor some of the molecular alterations typical of primary glioblastomas,[14] including EGFR amplification, chromosome 7 gain and chromosome 10 loss.[4]

Besides being essential for nosological purposes, molecular subgroups also provide solid prognostic estimates: IDH-mutant gliomas with the 1p/19q codeletion are associated with the longest overall survival, followed by IDH-mutant gliomas without the 1p/19 codeletion and by IDH-wildtype gliomas.[4,5] Molecular subgroups ultimately provide better prognostic estimates than histology alone.[4,15] However, WHO grading still retains a prognostic impact among tumors belonging to the same molecular subgroup,[5,16,17] and this should not be overlooked. Estimates for overall survival, according to molecular subgroup and WHO grade, are summarized in Table 1.[5,16,17] Median overall survival ultimately ranges from over 14 years in IDH-mutant gliomas with 1p/19q codeletion to <2 years in IDH-wildtype gliomas (WHO grade III), reflecting the extreme biological heterogeneity of lower-grade gliomas.

Prognostic factors

As seen from the above molecular classification, molecular profile has an essential role in prognostic stratification in lower-grade gliomas. The prognostic and predictive value of the IDH mutation and the chromosome 1p/19q codeletion were first suggested by early studies[18–20] and were later confirmed by the results from EORTC, RTOG and NOA trials.[21–24] IDH-mutant gliomas are intrinsically associated with longer overall survival[18] and better response to alkylating agents,[19,20] and these characteristics are even more prominent in the subgroup of tumors harboring the 1p/19q codeletion. By contrast, IDH-wildtype gliomas confer much poorer prognosis compared with their IDH-mutant counterparts,[13] and display limited chemosensitivity except for tumors with MGMT promoter methylation.[25]

Besides molecular profile and WHO grading, several other patient and tumor characteristics have shown a prognostic value. In grade II diffuse gliomas older age (⩾40 years) at diagnosis, astrocytoma histology, larger preoperative tumor diameter (⩾6 cm), tumor crossing the midline, and presence of neurological deficits before surgery were all associated with poorer overall survival in a pooled analysis from EORTC 22844 and 22845 trials.[26] Similar data with regard to age, neurological deficits, Karnofsky performance status (KPS) and tumor diameter at diagnosis were obtained in other studies.[24,27–29] In anaplastic gliomas, age and KPS are the two main prognostic factors to consider, besides molecular profile, when planning individual treatment strategies.[24,30]

Surgery

Surgery is an inescapable step to reach histological diagnosis and acquire valuable molecular information. In grade II gliomas, early resection when possible should be preferred to watchful waiting.[31] Resection should be as extensive as possible, intraoperative imaging techniques, continuous electrophysiological monitoring and awake surgery minimizing surgical risks.[30] The extent of surgical resection correlates with both

progression-free survival (PFS) and overall survival (OS): patients undergoing gross total resection survive longer than patients having partial resection or biopsy.[28,32,33] This observation is consistent across studies, although we still do not dispose of randomized controlled trials in patients with low-grade gliomas.[32] The biological profile of the tumor has been hypothesized to influence its resectability: IDH-mutant gliomas could be susceptible to more radical resections, being less infiltrative.[34] Due to the favorable implications of extended resection, some authors encourage supratotal resection (i.e. beyond visible tumor margins).[35] Besides increasing patient survival, surgical resection can dramatically improve seizure control.[28]

In anaplastic gliomas, resection is systematic whenever possible, and fluorescence-guided surgery using 5-aminolevulinic acid may help to resect anaplastic foci. It may also be important to alleviate mass effect in patients with large neoplasms and to reduce tumor volume for subsequent irradiation. For all these reasons, surgery has enormous implications in both grade II and III gliomas, and patients should be referred to neurosurgeons specialized in the treatment of diffuse gliomas.[30]

Adjuvant therapies

The standard of adjuvant care for patients with lower-grade gliomas has recently been remodeled based on the long-term results of several phase III EORTC/RTOG clinical trials started in the late 1990s (Table 2).

Diffuse low-grade gliomas (WHO grade II)

Common treatment options include radiotherapy (50–54 Gray in 1.8 Gray/fraction), chemotherapy with temozolomide or procarbazine, lomustine and vincristine (PCV) and combined approaches. Systematic adjuvant *versus* delayed radiotherapy did not result in a gain of survival in grade II gliomas.[40] Therefore, for patients younger than 40 years old with macroscopically resected WHO grade II glioma, there is a consensus for strict radiological follow up (i.e. MRI scans every 3 months) without adjuvant treatment.[30,41,42] Adjuvant therapies are usually reserved for patients with residual tumor after surgery and/or unfavorable prognostic characteristics (e.g. age $>$ 40 years, neurological deficits, uncontrolled seizures).[30,41–43]

The RTOG 9802 study compared radiotherapy alone *versus* radiotherapy followed by PCV chemotherapy in patients with high-risk low-grade gliomas.[36,44] The long-term results of this trial[44] showed a clear benefit on both PFS and OS in the arm receiving radiotherapy plus PCV, with a gain of 5.5 years on survival (13.3 *versus* 7.8 years). Beneficial effect was more prominent in patients with IDH mutation and in those with oligodendroglioma histology. While this study does not indicate when the radiotherapy should be performed, it clearly demonstrates that radiotherapy should be systematically associated with PCV chemotherapy.

Other trials explored the possibility to delay radiotherapy until progression to avoid the detrimental effects of radiotherapy on cognitive function.[45–47] The EORTC 22033 study compared upfront radiotherapy *versus* dose-dense temozolomide (75 mg/m^2 daily on a 21/28 days scheme) in high-risk WHO grade II gliomas. An initial report published in 2016[23] after a median follow up of 48 months showed no significant differences between treatment groups in terms of PFS, except for the subgroup of patients with IDH-mutant 1p/19q non-codeleted gliomas, who had a better PFS with radiotherapy compared to chemotherapy. Data on OS are not yet available.

In patients with high-risk grade II gliomas, these data suggest that IDH-mutant astrocytomas should receive upfront radiotherapy with adjuvant PCV. However, a common attitude in IDH-mutant, 1p/19q codeleted oligodendrogliomas is to administer upfront chemotherapy and reserve radiotherapy for progression, in consideration of their indolent evolution and remarkable chemosensitivity.[48,49] Treatment strategies in IDH-wildtype astrocytomas are still ill-defined owing to lack of adequate class of evidence, and the extreme heterogeneity of this group. Treatment should be decided on a case-by-case basis, based on prognostic factors including age, KPS, gain of chromosome 7 and loss of chromosome 10, clinical and radiological course, and MGMT methylation status.[30] A radiochemotherapy regimen with concomitant and adjuvant temozolomide is often proposed in these patients but has never been evaluated.

Anaplastic gliomas (WHO grade III)

The need for adjuvant therapies in anaplastic gliomas after surgical resection is well established.

Table 2. Phase III trials evaluating the role of adjuvant chemotherapy in grade II and III gliomas.

		Whole cohort						IDH-mutant (all)						IDH-mutant, 1p/19q codeleted						IDH-mutant, 1p/19q non-codeleted						IDH-wild type					
		PFS (yrs)	HR (95% CI)	*p* value	OS (yrs)	HR (95% CI)	*p* value	PFS (yrs)	HR (95% CI)	*p* value	OS (yrs)	HR (95% CI)	*p* value	PFS (yrs)	HR (95% CI)	*p* value	OS (yrs)	HR (95% CI)	*p* value	PFS (yrs)	HR (95% CI)	*p* value	OS (yrs)	HR (95% CI)	*p* value	PFS (yrs)	HR (95% CI)	*p* value	OS (yrs)	HR (95% CI)	*p* value
Diffuse low-grade gliomas (WHO grade II)																															
RTOG 9802[36]	RT (n = 126)	4.0	1	<**0.001**	7.8	1	**0.003**	≈ 4.6	1	<**0.001**	≈ 10.1	1	**0.02**	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
High-risk grade II gliomas	RT + PCV (n = 125)	10.4	**0.50 (0.36–0.68)**		13.3	**0.59 (0.42–0.83)**		NR	**0.32 (0.17–0.62)**		NR	**0.42 (0.20–0.86)**		na	na		na	na		na	na		na	na		na	na		na	na	
EORTC 22033[22]	RT (n = 240)	3.8	1	0.22	na	na	na	na	na	na	na	na	na	≈ 5.0	1	0.91	na	na	na	≈ 4.6	1	**0.0043**	na	na	na	≈ 1.6	1	0.24	na	na	na
High-risk grade II gliomas	TMZ (n = 237)	3.3	1.16 (0.9–1.5)		na	na		na	na		na	na		≈ 4.5	1.04 (0.56–1.93)		na	na		≈ 2.9	**1.86 (1.21–2.87)**		na	na		≈ 2.1	0.67 (0.34–1.32)		na	na	
Anaplastic gliomas (WHO grade III)																															
EORTC 26951[20]	RT (n = 183)	1.1	1	na	2.6	1	na	3.0	1	na	5.4	1	na	4.2	1	na	9.3	1	na	na	na	na	na	na	na	0.6	1	na	1.2	1	na
Anaplastic oligodendrogliomas	RT + PCV (n = 185)	2.0	**0.66 (0.52–0.83)**		3.5	**0.75 (0.60–0.95)**		5.9	**0.49 (0.29–0.84)**		NR	**0.53 (0.30–0.95)**		13.1	**0.42 (0.24–0.74)**		NR	0.56 (0.31–1.03)		na	na		na	na		0.8	**0.56 (0.37–0.86)**		1.6	0.78 (0.52–1.18)	
RTOG 9402[21,37,38]	RT (n = 143)	1.7	1	**0.004**	4.6	1	0.1	na	na	na	5.7	1	**0.006**	2.9	1	<**0.001**	6.8	1	**0.01**	na	na	na	3.3	1	**0.045**	na	na	na	1.8	1	0.67
Anaplastic oligodendrogliomas	RT + PCV (n = 148)	2.6	**0.69 (0.52–0.91)**		4.7	0.79 (0.60–1.04)		na	na		9.4	**0.59 (0.40–0.86)**		8.4	**0.47 (0.30–0.72)**		14.7	**0.49 (0.28–0.85)**		na	na		5.5	**0.56 (0.32–0.99)**		na	na		1.3	1.14 (0.63–2.04)	
CATNON[39]	RT, no adj TMZ (n = 372)	1.6	1	na	3.4	1	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Non-codeleted anaplastic gliomas	RT + adj TMZ (n = 373)	3.6	**0.62 (0.50–0.76)**		NR	**0.65 (0.45–0.93)**		na	na		na	na		na	na		na	na		na	na		na	na		na	na		na	na	

adj, adjuvant; HR, hazard ratio; na, not available; NR, not reached; OS, overall survival; PCV, procarbazine, lomustine and vincristine; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide; yrs, years.

Radiotherapy has been widely used as adjuvant treatment in anaplastic gliomas (59.4–60 Gray in 1.8–2.0 Gray/fraction), alone or in combination with chemotherapy.[30,37,41,43,50,51]

Two distinct phase III clinical trials addressed the clinical value of adjuvant PCV chemotherapy associated with radiation in anaplastic oligodendrogliomas (EORTC 26951 and RTOG 9402). The EORTC 26951 study[21] compared radiotherapy alone *versus* radiotherapy followed by six cycles of adjuvant PCV. The RTOG 9402 study[38,39] compared radiotherapy alone *versus* four cycles of intensified PCV regimen followed by radiotherapy. Both studies reached the same conclusions and the same trends. Globally, patients in the PCV arm showed longer PFS and OS (hazard ratio = 0.75) in both studies compared to patients treated with radiotherapy alone. When considering the three molecular subgroups separately, patients with IDH mutation and 1p/19q codeletion showed a strong benefit from PCV chemotherapy, which resulted in dramatically improved OS (from 7 to 14 years).[21,22] Patients with IDH mutation but no 1p/19q codeletion in the PCV arm showed a milder benefit in OS, but still significant in the RTOG study (from 3.3 to 5.5 years).[21,38] It is, therefore, recommended to associate adjuvant chemotherapy to radiotherapy in IDH-mutated gliomas. By contrast, there was no benefit of PCV in the IDH-wildtype group. The CATNON trial[52] evaluated the benefit of concomitant and/or adjuvant temozolomide in non-codeleted grade III gliomas. A preliminary and still incomplete analysis demonstrates that 12 cycles of adjuvant temozolomide improved both PFS and OS, compared to radiotherapy alone. Full and more mature data are expected in the near future with the analysis of concomitant temozolomide and the analysis of the IDH status, which will be helpful to understand whether this survival benefit is restricted (or not) to IDH-mutant cases.

To summarize, there is a general consensus that 1p/19q codeleted anaplastic oligodendrogliomas should receive radiation with adjuvant PCV chemotherapy. The advised treatment scheme for IDH-mutant non-codeleted anaplastic astrocytomas includes radiation followed either by PCV, based on RTOG study,[22,38,39] or by temozolomide, based on the preliminary results of the CATNON trial.[52] While the final analysis of the CATNON trial is expected, there is a common attitude to treat IDH-wildtype anaplastic astrocytomas with concomitant radiochemotherapy with temozolomide followed by adjuvant temozolomide, as they ultimately behave as primary glioblastomas.[15]

Current controversies

In the neuro-oncology community, a debate is currently ongoing on whether the PCV regimen could be replaced by temozolomide.[53,54] PCV chemotherapy was the standard of care when the large phase III EORTC/RTOG trials were planned. Temozolomide is indeed easier to administrate and less toxic than PCV chemotherapy.[55] As a result, in recent years temozolomide has been widely used in lower-grade gliomas,[56,57] even in the absence of class I evidence. However, PCV has been shown to induce prolonged responses with ongoing decrease of tumor size several years after the end of the PCV,[58] and could also have a higher efficacy.[24,59] While the NOA-04 trial[24,55] may suggest a superiority of PCV over temozolomide, this study was not powered to show a difference between the two regimens. Direct comparisons between PCV and temozolomide (in addition to radiotherapy) will be provided by the ongoing CODEL trial [ClinicalTrials.gov identifier: NCT00887146], which is now a two-arm study comparing radiotherapy plus PCV *versus* radiotherapy plus concomitant and adjuvant temozolomide in 1p/19q codeleted anaplastic oligodendrogliomas.

Another debated topic is the timing of radiotherapy (now associated with PCV; see above) in patients with long-term survival expectancy (i.e. grade II and 1p19q codeleted gliomas), because of the long-term toxicity.[45–47] In grade II gliomas, it is well established that radiotherapy, in contrast to chemotherapy, severely compromises brain plasticity and this should be taken into account when considering future surgeries. For this reason, a neoadjuvant chemotherapy (usually with temozolomide) may be discussed: first, it may delay the timing of radiotherapy-PCV; second, it may open the door to a subsequent surgery because of the reduction of the mass, and also because of the neural remodeling allowing resection of an area that was previously shown to be functionally important. Therefore, in grade II gliomas, the timing of radiotherapy should be carefully discussed for each individual patient within the multidisciplinary team.[60,61]

The EORTC 26951 and the RTOG 9402 trials showed that anaplastic oligodendrogliomas should also receive PCV chemotherapy besides radiation. The longer survival and increased chemosensitivity of 1p/19q codeleted gliomas inevitably raises the question of whether these patients could receive PCV chemotherapy only, postponing radiation. This strategy aims at sparing patients as long as possible of the cognitive deterioration associated with brain irradiation.[45–47] The ongoing POLCA trial [ClinicalTrials.gov identifier: NCT02444000] comparing PCV alone *versus* radiotherapy followed by PCV in patients with anaplastic codeleted oligodendrogliomas should answer this question.

Recurrent disease

In patients with WHO grade II or III gliomas progressing after radiotherapy and chemotherapy, options include surgical reintervention, second-line chemotherapies and, in rare cases, stereotactic radiotherapy.[37,51] Whenever possible, the inclusion in clinical trials for target therapies should be encouraged. Individual treatment should ultimately be chosen based on tumor characteristics at recurrence, previous treatment modalities, patient age and KPS.

Surgical reintervention has been shown to prolong survival in several retrospective studies, especially in grade II gliomas.[62,63] In the case of a compressive tumor, it is effective in relieving patients' symptoms. Furthermore, it can provide tumor tissue for histological examination (malignant progression) and molecular testing for actionable targets. Radiosurgery may be proposed to target small nodular lesions, and can be used even in previously irradiated patients.[64–66] Second-line chemotherapies include temozolomide, which can be administered according to the standard,[67,68] metronomic[69] or dose-dense[70,71] schedule, and nitrosoureas (including lomustine, carmustine and fotemustine), depending on the chemotherapy used at first line.

The antiangiogenic agent bevacizumab has been extensively used in past years (first in combination with irinotecan,[72,73] then alone[74,75] since the combination did not prove any significant benefit) and provided a high response rate and symptomatic clinical improvement. However, the recent phase II trial (TAVAREC) showed that the addition of bevacizumab to temozolomide failed to improve both PFS and 12-month OS in recurrent grade II and III gliomas.[76]

Target therapies

Despite the advances in the treatment of diffuse gliomas, no therapy is curative and tumors will eventually recur. Nevertheless, recent discoveries led to a better understanding of the biological mechanisms underlying gliomagenesis and to the identification of molecular alterations susceptible to target therapy.

The IDH mutation is a promising therapeutic target[77] as it is tumor-specific and uniformly expressed in tumor cells.[78,79] Several approaches are currently being explored in this regard, including inhibiting the mutant form of the IDH enzyme or targeting the epigenetic changes induced by its neomorphic function. The mutant IDH enzyme leads to the intracellular accumulation of 2-hydroxyglutarate,[80] an oncometabolite that blocks cell differentiation by inducing DNA hypermethylation (CpG island methylator phenotype).[81] IDH1/2 selective inhibitors, reducing the levels of 2-hydroxyglutarate by blocking mutant enzyme activity, reverse DNA hypermethylation and promote cell differentiation. Following the results obtained in preclinical models,[82–84] IDH-inhibitors are now being investigated in phase I/II clinical trials [ClinicalTrials.gov identifier: NCT02073994, NCT02273739, NCT02481154, NCT02977689, NCT02746081].

Differentiating therapies and demethylating agents have been proposed as alternative strategies to counteract the epigenetic changes induced by the accumulation of 2-hydroxyglutarate. In xenograft models, the administration of demethylating agents reduced DNA methylation, increased cell differentiation and reduced tumor growth.[85,86] A phase I trial of azacytidine in solid malignancies, including glioblastoma, is currently recruiting [ClinicalTrials.gov identifier: NCT02223052].

Vaccination against the mutant IDH enzyme is another strategy currently being explored. In animal models, peptide vaccines were able to elicit a mutation-specific T-helper response against the IDH-mutant enzyme.[87,88] Ongoing phase I trials are now testing peptide vaccines against R132H IDH1 in recurrent grade II [ClinicalTrials.gov identifier: NCT02193347] and grades III–IV gliomas [ClinicalTrials.gov identifier: NCT02454634].

Poly-ADP-ribose-polymerase (PARP) inhibitors have recently been proposed for the treatment of diffuse gliomas. By inhibiting PARP enzymatic activity, these agents prevent the repair of DNA single-strand breaks, increasing the efficacy of cytotoxic treatments. IDH-mutant gliomas appear especially sensitive to PARP inhibitors, as these tumors are characterized by an intrinsic homologous recombination defect induced by 2-hydroxyglutarate accumulation.[89,90] PARP inhibitors, either alone or in combination with alkylating chemotherapies, have shown powerful anticancer activity in preclinical models.[89,90] A phase I clinical trial using the PARP inhibitor olaparib (in association to temozolomide) in recurrent glioblastomas is ongoing [ClinicalTrials.gov identifier: NCT01390571], and trials in lower-grade gliomas are under design.

Interestingly, gliomas – especially IDH-mutant non-codeleted astrocytomas – may develop a mismatch repair (MMR) deficiency (due to inactivating mutation of MMR genes, *MLH1, MSH2, MLH5, PMS2* or *PolE*) as a mechanism of resistance to alkylants, resulting in a hypermutated genome.[91–93] MMR-deficient patients have a highly immunogenic tumor.[94] Indeed, the deficient DNA repair mechanism in MMR results in higher mutational load and neoantigen load in these tumors, which appear as good candidates for checkpoint inhibitor immunotherapy. These therapies revolutionized the treatment of melanoma[95] and other systemic neoplasms, triggering the anti-tumor immune response and reversing the state of local immune suppression promoted by the tumor itself. Preclinical studies showed efficacy of both CTLA-4 and PD-1 blockade in glioma murine models.[96,97] Durable responses to the anti-PD1 agent nivolumab have been reported in two children with glioblastoma and constitutive MMR deficiency.[98] Several trials are currently exploring the use of checkpoint inhibitors in high-grade gliomas (recently reviewed by Zhang[99]). Initial results from the BMS CheckMate-143 trial do not show improved OS following nivolumab treatment in recurrent glioblastoma.[100] However, future trials should specifically focus on a selected population of gliomas with either constitutive or acquired MMR deficiency.[101]

The therapeutic armamentarium for IDH-wildtype grade II and III gliomas is unfortunately less developed. The need for new treatment options is very strong in this subgroup, as these neoplasms are associated with malignant behavior and limited response to adjuvant therapies. IDH-wildtype WHO grade II and III gliomas may, in a proportion of cases, harbor molecular alterations typical of primary glioblastomas. They should thus be investigated for the presence of these molecular alterations and especially for the ones susceptible of target therapy (EGFR amplification,[102] BRAF V600E mutation[103]). The *FGFR–TACC* gene fusion, first discovered in glioblastomas,[104] is detected in about 3% of IDH-wildtype grade II and III gliomas.[105,106] The transcript fusion protein is homogeneously expressed within the tumor and always retains the FGFR tyrosine kinase domain, representing thus an ideal target for FGFR inhibition. First reports showed clinical response, following the administration of the FGFR inhibitor AZD4547, in two patients with glioblastomas harboring the *FGFR–TACC* fusion.[105] FGFR inhibition is currently being tested in recurrent gliomas with the *FGFR–TACC* fusion [EUDRACT 2014-005428-81; ClinicalTrials.gov identifier: NCT01975701].

Conclusions

WHO grade II and III gliomas form a heterogeneous group of neoplasms, and treatment strategies should be individualized based on patient and tumor characteristics, and particularly molecular characteristics. The long-term results of large international trials started in the 1990s recently allowed establishment of general treatment schemes based on WHO grade and molecular profile. However, the IDH-wildtype grade II gliomas remain probably the group most in need of guidelines. Consideration of the risk for long-term neurotoxicity is mandatory in patients with long life expectancy, such as IDH-mutant codeleted patients, and the opportunity to delay radiotherapy in this population is currently the object of investigation.

The use of target therapies is at present restricted to clinical trials, but should hopefully enter clinical practice in the future. Depending on the molecular characteristics of the tumor, inclusion in these clinical trials should be encouraged at recurrence. MMR deficiency can be present in gliomas recurring after alkylant therapy, raising the possibility of immune checkpoint inhibitor treatments in these patients. Loss of expression of MMR proteins should therefore be systematically investigated in patients who are candidates for surgery at recurrence.

Key points

- Median OS depends on molecular profile (IDH-mutant, 1p/19q codeleted; IDH-mutant, 1p/19q non-codeleted; IDH-wildtype) ranging from over 15 years to <2 years.
- Besides molecular profile and WHO grade, the main prognostic factors include age, KPS, presence of neurological deficits at diagnosis and preoperative tumor diameter.
- Surgery has a capital role in the treatment of grade II gliomas, as the extent of resection correlates with patient survival.
- Low-risk patients with grade II gliomas can undergo strict radiological follow up without adjuvant therapies if treated with macroscopic total resection. High-risk patients should instead receive adjuvant treatment with radiotherapy and PCV.
- Patients with anaplastic gliomas (WHO grade III) need adjuvant therapies after surgery, associating radiation and chemotherapy (adjuvant PCV or concomitant and adjuvant temozolomide depending on the molecular subtype).
- Treatment options at recurrence include surgical reintervention, chemotherapy and irradiation. Whenever possible, the inclusion in clinical trials for target therapies should be encouraged.
- Innovative target therapies are being tested, including IDH-inhibitors, PARP inhibitors and mutation-specific vaccines for IDH-mutant gliomas, and immune checkpoint inhibitors in recurrent gliomas with MMR deficiency.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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