EXPERT REVIEWS

Anaplastic glioma: current treatment and management

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Anaplastic glioma (AG) is divided into three morphology-based groups (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma) as well as three molecular groups (glioma-CpG island methylation phenotype [G-CIMP] negative, G-CIMP positive non-1p19q codeleted tumors and G-CIMP positive codeleted tumors). The RTOG 9402 and EORTC 26951 trials established radiotherapy plus (procarbazine, lomustine, vincristine) chemotherapy as the standard of care in 1p/19q codeleted AG. Uni- or non-codeleted AG are currently best treated with radiotherapy only or alkylator-based chemotherapy only as determined by the NOA-04 trial. Maturation of NOA-04 and results of the currently accruing studies, CODEL (for codeleted AG) and CATNON (for uni or non-codeleted AG), will likely refine current up-front treatment recommendations for AG.

KEYWORDS: 1p/19q codeletion • anaplastic glioma • ATRX • bevacizumab • chemotherapy • IDH1 • MGMT promoter methylation • molecular biomarkers • nitrosourea • radiotherapy • temozolomide

Anaplastic glioma (AG) comprise 6–15% of all primary brain tumors [1,2]. Three histological subtypes are characterized: anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA). Molecular biomarkers, such as IDH1 (isocitrate dehydrogenase 1 gene), G-CIMP (glioma-CpG island methylation phenotype), 1p19q chromosome codeletion and ARTX (α-thalassemia/mental retardation X-linked gene), are increasingly becoming an integral part of the diagnosis and have helped to redefine gliomas [3–6]. AG are predominantly hyperintense intraparenchymal lesions by T2-weighted and fluid attenuated inversion recovery (FLAIR) MRI often demonstrating enhancement after contrast administration. However, in up to 30% of cases, no enhancement is seen [7]. Median overall survival of AG varies widely from 2 to 12 years [8–11]. Good prognostic features include preserved functional status (high performance score with limited neurological deficits), young age, a complete surgical resection and oligodendroglial histology [11–16]. The 1p/19q codeletion was first identified as both a prognostic and predictive biomarker in the EORTC (European Organization for Research and Treatment of Cancer) 26951 and RTOG (Radiation Therapy Oncology Group) 9402 trials [9,10,17,18]. A recursive partitioning analysis of AG identified five prognostic subtypes using three variables (age, 1p19q codeletion status and tumor location): class I (age < 60 years, 1p19q codeleted), class II (age < 43 years, not codeleted), class III (age 43–59 years, not codeleted, frontal lobe tumors or age ≥ 60 years, codeleted), class IV (age 43–59 years, not codeleted, not frontal lobe tumor or age 60–69 years, not codeleted) and class V (age ≥70 years, not codeleted). Survival varied from 0.6 years for class V to 9.3 years for class I tumors [19]. The most significant prognostic variable was age defined as <60 or ≥ 60 years. Nonetheless large variability in survival was observed between the three histological subgroups of AG. Moreover, the outcome and the response to therapy of histologically identical tumors often is very different [3,19]. Several biological markers including 1p/19q codeletion, mutation of IDH1, presence of the G-CIMP, MGMT (methylguanine methyltransferase) promoter methylation, ATRX mutation, TERT (telomerase reverse transcriptase) promoter mutation, p53 mutation, PTEN (phosphatase and tensin homolog) mutation, EGFR (epidermal growth factor receptor) and PDGFR (platelet derived growth factor receptor) overexpression or amplification and gene expression profiles have been identified as potential prognostic factors in AG [16,20]. In the German NOA-4 trial, AO and AOA demonstrated a better prognosis than AA [11]. Among AA, tumors with a loss of ATRX and IDH1 appear to have a more

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favorable prognosis than wildtype counterparts in the RTOG 9402 trial [4].

Initial treatment includes, as in all gliomas, maximal safe resection [7,21]. The management after initial surgery of AG with 1p/19q codeletion includes radiotherapy (RT) and PCV (procarbazine, CCNU, vincristine) chemotherapy as established by the EORTC 29651 and RTOG 9402 trials. The treatment of uni- or nondeleted AG is either RT only or primary alkylator-based chemotherapy only with deferred RT as determined in the NOA-04 trial. A new classification using molecular markers may improve the initial management of AG and tailor treatment according to the presence or absence of prognostic markers as mentioned above [20].

Histology & molecular biology

Histology

The 2007 WHO classification of gliomas currently uses only morphological criteria [22] and defines three groups. AO and AOA account for 30–50% of all AG, the remaining 50–70% are defined as AA [23]. The WHO classification has been validated as having prognostic value [11]. Nevertheless, the WHO classification is prone to high interobservator variability among the subtypes of AG as well as pathology discordance between grades of glioma [7,24–27].

Molecular biomarkers add diagnostic, prognostic and predictive value to the morphological classification and increasingly influence treatment decision. By example, AO mostly are characterized by 1p/19q codeletion, the hypermethylation phenotype (G-CIMP positive), TERT promoter mutation and IDH1 mutation and have the best prognosis among AG. By contrast, AA lack the 1p/19 codeletion, are mutated in p53, ATRX and IDH1 and have the poorest prognosis among AG [28].

Molecular biology

IDH mutations

IDH1 or less commonly IDH2 mutations are present in 50–83% of AG with the highest prevalence in AO [16,25,29–33]. IDH mutations are predominantly in IDH1 (R132H). IDH2 (R172H) mutations represent only 3% of all IDH mutations. Either IDH mutation is commonly associated with oligodendroglial histology [29,34]. In the NOA-04 trial, IDH1 mutations were detected in 65.6% of all patients (71% of AO, 73% of AOA and 57% of AA (Table 1) [11]. In the EORTC 26951 trial, IDH1 mutations were observed in 46% of the patients with a confirmed AO after central review [10]. In the EORTC 26951 trial, IDH2 mutations were observed in only 0.6% of the AO and AOA tumors (Table 1) [33].

Notably, the IDH mutational status does not change during disease evolution [35]. The IDH mutation is responsible of epigenetic remodeling [3,25,36] that results in the hypermethylation phenotype, i.e., G-CIMP positive [37]. Patients with G-CIMP-positive tumors have a longer survival [3,38,39] and are frequently co-associated with the 1p/19q codeletion (seen in 86% of G-CIMP-positive tumors in the EORTC 26951 trial) [3,10,16,36,40,38,39,41,42].

The significance of the IDH mutation and associated germline polymorphism (rs55705857) were identified in patients in the RTOG 9402 trial and were determined to be predictive in non-codeleted patients treated with RT + PCV. IDH mutations and the presence of the G risk allele were seen in 74 and 31% of the assessed tumors. Both were correlated with an improved progression-free survival (PFS) and the IDH mutation was correlated with longer overall survival (OS) as well. The authors postulated that a subset of non-codeleted patients with IDH mutation may survive longer after treatment with RT + PCV when compared to RT only (Table 2) [6].

IDH1 mutation appears to be the earliest mutation in gliomagenesis preceding the appearance of both 1p19q codeletion and the ATRX mutation [6,29]. IDH mutated and IDH wildtype tumors are associated with distinct clinical phenotypes. Patients with IDH mutations are younger across all glioma grades and the mutation is rarely seen in elderly patients [3,33,34]. Gliomas with IDH mutations are more frequently located in the frontal lobe and by MRI are often without necrosis and manifest no modest contrast enhancement [34,43]. Distant recurrences are more frequently observed in tumors without IDH mutations [31].

IDH1 mutations are more often observed in tumors with 1p/19q codeletion (up to 86%) and in tumors with MGMT promoter methylation (58–100% vs 10–26% in unmethylated tumors) [30,33,44,45]. Additionally, IDH is inversely correlated with unfavorable biomarkers such as EGFR amplification, polysomy of chromosome 7 and loss of chromosome 10 [33,46].

Retrospective studies [24,47,48] have shown that IDH mutation is a favorable marker in all subtypes of AG. Patients with AA without IDH mutation have been reported to have a better survival than patients with glioblastoma (GB) without IDH mutation, but a poorer survival than patients with AA and IDH mutations and patients with GB and IDH mutation [5]. The independent favorable prognostic significance of IDH mutation and 1p/19q codeletion has been shown in several studies [11,33,49].

Currently, however, there is no established predictive value of IDH mutation [16,25,33]. In IDH mutated tumors, MGMT promoter methylation has only a prognostic role, whereas in IDH wildtype tumors, MGMT promoter methylation has been shown to be a predictive marker for receipt of alkylating chemotherapy [6,50,51]. Increasing interest in the IDH1 mutation as a potential druggable target in glioma has recently been demonstrated *in vitro* [52–54].

1p/19q codeletion

1p/19q codeletion, an unbalanced translocation, is found in 40.9% of AG [11] and can be detected in 77% of AO, 59% of AOA and < 15% of AA [11,55]. In RTOG 9402, 1p/19q codeletion was noted in 76% of AO and 24% of AOA [9]. In EORTC 26951, 1p/19q codeletion was observed in 25% of AO/AOA (Table 1) [10]. In WHO Grade II/III oligodendrogliomas 1p/19q codeletion is present in 80–90%, and thus is considered a molecular signature of oligodendroglial tumors [56,57]. Like IDH mutational status, 1p/19q deletion status does not change during disease evolution [35,58]. The majority of 1p/19q codeleted tumors have a mutation of either IDH1 or

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Table 1. Prevalence of IDH mutation, 1p/19q codeletion and MGMT promoter methylation in NOA-04, EORTC 26951 and RTOG 9402 trials.

	Histology (centrally reviewed)	IDH	1p/19q	MGMT	Ref.
NOA-04 RT arm (n = 139) Wick *et al*. (2009)	AA: 70 AOA: 47 AO: 22	IDH1 Wildtype: 62 Mutated: 36 Missing: 41 IDH2 Wildtype: 94 Mutated: 4 Missing: 41	Codeleted: 41 Non-codeleted: 54 Missing: 44	Methylated: 59 Unmethylated: 44 Missing: 36	[11]
NOA-04 PCV or TMZ arm (n = 135) Wick *et al*. (2009)	AA: 74 AOA: 44 AO: 17	IDH1 Wildtype: 66 Mutated: 31 Missing: 38 IDH2 Wildtype: 95 Mutated: 2 Missing: 38	Codeleted: 33 Non-codeleted: 53 Missing: 49	Methylated: 64 Unmethylated: 35 Missing: 36	[11]
EORTC 26951 RT arm van den Bent *et al*. (2013)	183	IDH Wildtype: 50 Mutated: 36 Missing: 97	Codeleted: 37 Non-codeleted: 122 Missing: 24	Methylated: 62 Unmethylated: 24 Missing: 97	[10]
EORTC 26951 RT/PCV arm van den Bent *et al*. (2013)	185	IDH Wildtype: 47 Mutated: 45 Missing: 93	Codeleted: 43 Non-codeleted: 114 Missing: 28	Methylated: 74 Unmethylated: 23 Missing: 88	[10]
RTOG 9402 RT arm Cairncross *et al*. (2013) and (2014)	143	IDH Wildtype: 23 Mutated: 76 Missing: 44	Codeleted: 67 Non-codeleted: 61 Missing: 15	Methylated: ND Unmethylated: ND Missing: ND	[6,9]
RTOG 9402 RT/PCV arm Cairncross *et al*. (2013) and (2014)	148	IDH Wildtype: 31 Mutated: 80 Missing: 37	Codeleted: 59 Non-codeleted: 76 Missing: 13	Methylated: ND Unmethylated: ND Missing: ND	[6,9]

AA: Anaplastic astrocytoma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; IDH: Isocitrate dehydrogenase gene; 1p/19q:1: 19q codeletion; MGMT: Methylguanine methyltransferase; ND: Not detailed; PCV: Procarbazine, lomustine, vincristine; RT: Radiotherapy; TMZ: Temozolomide.

IDH2 [1,59] and frequently manifest MGMT promoter methylation [11,46]. AOA with 1p/19q codeletion are considered oligodendroglial tumors and classified as molecular AO [4].

The prognostic role of 1p/19q codeletion has been established in several studies in AG (Table 3) [9–11]. Tumors harboring 1p/19q have a better prognosis and longer survival [25,49,60]. Loss of 1p alone or 19q alone, so-called uni-deletion, is frequently seen but does not convey the same prognostic implication as codeletion [3,35]. Two randomized Phase III trials (RTOG 9402 and EORTC 26951) have further confirmed the predictive role of 1p/19q codeletion when treated with combined radiochemotherapy (RT + PCV). An overall survival benefit was observed only in AG treated with RT + PCV and in patients with 1p/19q codeleted tumors [9,10].

MGMT: O6-methylguanine DNA-methyltransferase (DNA damage repair enzyme).

In the NOA-04 study, methylation of the MGMT promoter (resulting in decreased intratumoral MGMT) was detected in 60.9% of the patients with AG (Table 1). MGMT promoter methylation was more common in AO (71%) and AOA (70.7%) than in AA (50%) [11]. Methylation of the MGMT promoter has been described in 75–80% of the AO and AOA [16,46]. Approximately 80–88% of AO with 1p/19q codeletion have a methylated MGMT promoter [46,61,62].

The MGMT promoter methylation is a robust prognostic factor associated with prolonged PFS and OS in high-grade gliomas [11,50,63,64]. Nevertheless, most studies have failed to demonstrate that MGMT methylation is predictive in AG [3,46]. In

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Table 2. Frequency and median overall survival of the different molecular markers in RTOG 9402 [6].

Anaplastic oligodendroglial tumors AO/AOA	Frequency (%)	Median overall survival (years)	
Molecular signature		*Radiotherapy*	*Radiotherapy + PCV*
IDH1 mutation	74	5.7	9.4
IDH wildtype	26	1.3	1.8
1p/19q codeleted + IDH1 mutation	42	6.8	14.7
Non 1p/19q codeleted + IDH1 mutation	32	3.3	5.5
ATRX mutation		2.7	11.0
ATRX wildtype		3.5	4.4
Non-1p/19q codeleted + IDH1 wildtype	21	1.0	1.3
1p/19q codeleted + IDH1 wildtype	5		

AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; ATRX: Alpha thalassemia mental retardation X-linked gene; IDH: Isocitrate dehydrogenase; PCV: Procarbazine, lomustine, vincristine.

the EORTC 26951 trial, MGMT promoter methylation was not predictive of response following either RT + PCV or RT only [16,46]. In a sub-study of 183 patients from the NOA-04 trial, MGMT and IDH1 status were analyzed for interdependency regarding a prognostic versus predictive role. The analyses showed that MGMT promoter methylation is a predictive marker for response to alkalyting chemotherapy in IDH wildtype tumors only and not in IDH mutated tumors [50,65].

ATRX

The loss of ATRX expression occurs predominantly in AA and AOA without 1p/19 codeletion [4]. ATRX loss is considered a specific marker for astrocytic lineage tumors [3,4,25]. In a sub-study of 133 patients in the NOA-04 trial, loss of ATRX expression was observed in 45% of AA, 27% of AOA and only 10% of AO [4]. In other cohorts, ATRX loss was found in 41–73% of AA [5,66,67].

In the NOA-04 study, ATRX status was associated with young age, astrocytic histology, IDH1 mutation, uni- or non1p/19q codeleted tumors, alternative lengthening of telomeres and MGMT promoter methylation. Loss of ATRX was mostly restricted to IDH mutant tumors and mutually exclusive with 1p/19q codeletion and TERT promoter mutation [4,25]. ATRX loss was observed in 65% of IDH mutated and 1p/19q intact tumors, 7% in 1p/19q codeleted tumors and 6% in IDH wildtype tumors. Patients with ATRX loss and IDH mutation were younger than patients with ATRX wildtype and IDH mutation or IDH and ATRX wildtype patients. In two other studies, a 70% prevalence of ATRX mutation was seen in 1p19q non-codeleted IDH mutated AG [5,66]. In another study, 46% of the AG expressed ATRX alteration and the prevalence of ATRX loss increased to 92% in AG manifesting a IDH mutation [68]. A close overlap ($p < 0.0001$) is seen between loss of ATRX expression and IDH1/2 mutation in AA. As well, longer survival is seen in patients with loss of ATRX expression as determined in the study by Cai [67]. In the NOA-4 cohort, patients with AG harboring ATRX loss had a significantly better prognosis than IDH mutated tumors that express ATRX [4]. The loss of ATRX expression appears to identify a more favorable subgroup of AG (Table 2) [3,4,6,69]. Within AOA, ATRX mutational status improves the morphology-based definition and distinguishes astrocytic AOA (defined by ATRX loss) from oligodendroglial AOA (defined by 1p19q codeletion). AOA defined by neither ATRX mutation nor 1p19q codeletion appear to have the worst outcome [4].

Intrinsic glioma subtypes

Six intrinsic glioma subtypes (IGS), each representing molecularly similar groups identified by an unsupervised gene expression analysis, have been identified after RNA extraction, purification and quantification from either fresh frozen or formalin-fixed and embedded in paraffin material. IGS has been shown to be a better predictor of survival than histology in large external data sets but not in large randomized trials [70,71].

In a subset of 140 patients enrolled into the EORTC 26951 trial, IGS was prognostic for PFS independent of clinical (age, performance status, tumor location) or molecular classification (1p/19q codeletion, IDH1 mutation, MGMT promoter methylation). The IGS-9 subtype, characterized by a majority of 1p/19q codeletion and IDH1 mutationed tumors, was predictive of a response to PCV chemotherapy [71].

CIC & FUBP1

Mutations of homolog of *Drosophila capicua* (CIC) and far-upstream binding protein 1 (FUBP1) are two tumor suppressor genes and acts as potent regulators of the cell growth. CIC is located on chromosomal arm 19q and FUBP1 on chromosomal arm 1p [69]. CIC and FUPB1 occur mostly in oligodendrogliomas in 46–53% (CIC) and 15–24% (FUBP1) respectively, but are far less common (<10%) in astrocytomas or oligoastrocytomas [69]. CIC mutations have been shown to be associated with oligodendroglioma histology, 1p/19q co-deletion and IDH1/2 mutation [72].

Jiao evaluated the mutational status of ATRX, CIC and FUBP1 in 363 gliomas. CIC and FUBP1 mutations were mostly observed in grade II (38 and 14% respectively) and grade III oligodendroglioma (52 and 31% respectively) but were rare in primary GB (1 and 2%, respectively) and absent in astrocytic grade II or III tumors. Only seven tumors had

Table 3. PFS and OS according to the 1p/19q codeletion status in the NOA-04, RTOG 94-02 and the EORTC 26951 trials.

	PFS	HR 95% CI p value	OS	HR 95% CI p-value
NOA-04 [11]				
RT arm	All AG: 30.6 months AA: 10.8 months AO/ AOA: 52.1 months	95% CI: 16.3–42.8 95% CI: 8.9–28.3 95% CI: 36.5 to NR	72.1 months	
PCV or TMZ arm	All AG: 31.9 months AA: 18.2 months AO/ AOA: 52.7 months	95% CI: 21.1–37.3 95% CI: 12.1–24.2 95% CI: 33.9 to NR	82.6 months	
RTOG 94-02 [9]				
Whole population (n = 291)				
RT alone arm (n = 143)	ND	HR: 0.68 95% CI: 0.53–0.88 p = 0.003	4.7 years	HR: 0.79 95% CI: 0.60–1.04 p = 0.1
PCV/RT arm (n = 148)	ND		4.6 years	
1p/19q codeleted patients (n = 126)				
RT alone arm (n = 67)	2.9 years	HR: 0.47 95% CI: 0.30–0.72 p < 0.001	7.3 years	HR: 0.59 95% CI: 0.37–0.95 p = 0.03
PCV/RT arm (n = 59)	8.4 years		14.7 years	
Non-1p/19q codeleted patients (n = 137) (50% of the entire cohort)				
RT alone arm (n = 61)	1.0 years	HR: 0.81 95% CI: 0.56–1.16 p = 0.24	2.7 years	HR: 0.85; 95% CI: 0.58–1.23 p = 0.39
PCV/RT arm (n = 76)	1.2 years		2.6 years	
EORTC 26951 [10]				
Whole population (n = 368)				
RT alone arm (n = 183)	13.2 months	HR: 0.66 ; 95% CI: 0.52–0.83 p = 0.003	30.6 months	HR: 0.75 ; 95% CI: 0.60–0.95 p = 0.018
RT/PCV arm (n = 185)	24.3 months		42.3 months	
1p/19q codeleted patients (n = 80) (25% of the entire cohort)				
RT alone arm (n = 37)	49.9 months	HR: 0.42; 95% CI: 0.24–0.74 p = 0.002	111.8 months	HR: 0.56 ; 95% CI: 0.31–1.03 p = 0.059
RT/PCV arm (n = 43)	156.8 months		Not reached	
Non-1p/19q codeleted patients (n = 236)				
RT alone arm (n= 122)	8.7 months	HR: 0.73 ; 95% CI: 0.56–0.97 p = 0.026	21.1 months	HR: 0.83 ; 95% CI: 0.62–1.10 p = 0.185
RT/PCV arm (n = 114)	14.8 months		25 months	

AA: Anaplastic astrocytoma; All AG: All anaplastic glioma subtypes; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; HR: Hazard ratio; n: Number of patients; NR: Not reached; OS: Overall survival; PCV: Procarbazine, lomustine, vincristine; PFS: Progression-free survival; RT: Radiotherapy.

concurrent CIC and FUBP1 mutations. In this cohort as in others, an IDH mutation was observed in every glioma with either CIC or FUBP1 mutation [69,73]. In the cohort of Jiao, 1p/19q codeletion was also found in nearly all glioma with CIC or FUBP1 mutation. CIC and FUBP1 mutations were mutually exclusive with ATRX or TP53 mutations. Thus, the authors categorized tumors harboring IDH1/2 mutations, 1p/19q codeletion, CIC mutation and FUBP1 mutation as I-C gliomas. These tumors typically had an oligodendroglial component. By contrast, I-A gliomas were defined by ATRX and TP53 mutations and have typically an astrocytic component. This genetic signature may help to distinguish clinically distinct subgroups of gliomas with differing prognosis and therapeutic implications; nevertheless further validation is needed before implementation into clinical practice.

TERT mutation

Maintenance of telomere length is a key oncogenic event in most cancers including gliomas.

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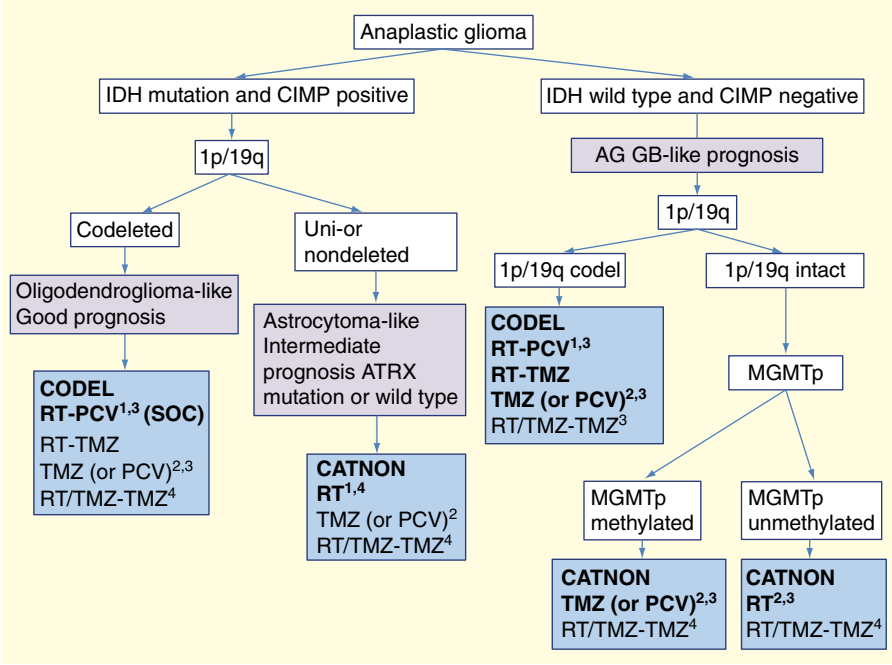

Figure 1. Molecular classification of AG, prognostic implications and therapeutic options for newly diagnosed anaplastic gliomas (adapted from Siegal 2014 and Wick 2015).

†based on the RTOG 9402 and EORTC 26951 trials.
‡based on NOA 04 trial.
§arm of the CODEL trial.
¶arm of the CATNON trial.
1p/19q codel: 1p/19q codeletion; AG: Anaplastic glioma; ATRX: α thalassemia mental retardation X-linked gene; CIMP: CpG island methylation phenotype; GBM: Glioblastoma; IDH: Isocitrate dehydrogenase; MGMT p: Methylguanine methyltransferase promoter; methyl: methylated; unmethyl: unmethylated; PCV: Procarbazine, lomustine, vincristine; RT - PCV: RT followed by PCV; RT – TMZ: RT followed by TMZ; RT/TMZ – TMZ: radiotherapy + concomitant and adjuvant TMZ; RT: Radiotherapy; SOC: Standard of care; TMZ: Temozolomide.

The telomerase reverse transcriptase (TERT) is involved in the tumor cell telomere maintenance. Increased telomerase expression may result from point mutations in the promoter of the TERT gene or due to mutations of telomere binding proteins (such as mutation of ATRX or death domain associated protein DAXX; neither involves telomerase directly and are termed alternative telomere lengthening) [4,74]. Mutations of the promoter of TERT are frequent among primary GB (70%) and pure oligodendroglial tumors (74%), but less often observed in diffuse astrocytoma (19%) and AA (25%) [74]. TERT promoter mutations are observed in almost all 1p/19q codeleted tumors [4,75]. TERT and ATRX mutations are mutually exclusive [74]. Further studies are needed to determine the prognostic role of TERT promoter methylation in gliomas.

New molecular classification of AG

The 1p/19q codeletion was the first molecular marker recommended to be used for therapeutic stratification of AG [76]. It is now recognized that the evaluation of the IDH mutation, 1p19q codeletion, MGMT promoter methylation and ATRX expression may further improve the morphology-based WHO classification and have direct clinical relevance [3,20,65,77]. There is a growing consensus distinguishing AG according to molecular characteristics. Several authors have suggested an initial segregation of AG subtypes according to the IDH/G-CIMP status followed by a further stratification according to the 1p/19q status [3,20,25]. In this algorithm, three clinically relevant groups of AG have been defined (Figure 1). In the IDH wild-type group of AG, MGMT promoter methylation status assists in determining the benefit of alkylating chemotherapy [3,20,50,77,78]. In this classification as increasingly recognized by others, AOA do not constitute a separate biological entity but rather are distinguished and separable by 1p19q codeletion and ATRX expression [4].

Treatment

Up-front treatment

Maximum safe resection is recommended as initial therapy in AG based upon general consensus despite the lack of prospective data [7,20,21,55]. A prognostic role regarding the extent of resection has been demonstrated retrospectively in most trials of AG [13]. In a retrospective cohort of 335 high-grade gliomas, aggressive surgical resection beyond the enhanced tumor margins conferred a longer survival in IDH mutated tumors only [79]. Surgery by removing mass and improving mass-related symptoms also allows the potential for rapid functional improvement of the patient [80]. Even in instances where a safe resection of an AG is not possible, tissue obtained by biopsy is still required to provide a precise histological and molecular diagnosis that guides management [20].

Treatment following initial surgery varies according to the histological type, molecular subtype and the clinical status of the patient. RT (54–60 Gy) has long been considered standard of care in all AG. Additionally, AO tumors have been demonstrated to be chemoresponsive to both nitrosoureas and temozolomide (TMZ) chemotherapy (CT) in up to 70% of the patients [7,20,60,81–86]. Based upon these observations, three randomized prospective trials have evaluated the up-front role of RT and CT in AG.

Adjuvant randomized trials in AG

The NOA-04 trial, a prospective randomized trial for newly diagnosed AG that included all subtypes, compared the efficacy and

safety of RT (60 Gy) followed by CT at progression with the reverse treatment sequence (Table 3) [11]. In this study, 274 patients were randomly assigned 2:1:1 between arm A (RT only, n = 139), arm B1 (PCV only, n = 68) and arm B2 (standard dose TMZ only, n = 67). At progression or at occurrence of unacceptable toxicity, patients in arm A were treated with PCV or TMZ (1:1 randomization), whereas patients in arms B1 or B2 were treated with RT. The primary endpoint was the time to tumor failure defined as progression after RT and one CT in either sequence. No difference was observed between patients treated with PCV or TMZ in median time to tumor failure (HR: 1.2, p = 0.28), PFS (HR: 1.0, p = 0.87) and OS; nevertheless TMZ was better tolerated. This study suggested a prognostic role for the extent of resection in AG and demonstrated that AOA and AO had a better prognosis compared to AA. Additionally, the presence of MGMT promoter methylation and IDH mutation was associated with a better prognosis. When comparing biomarkers, IDH mutation conferred the strongest prognostic value when compared to MGMT promoter methylation or 1p/19q codeletion [11]. Importantly and for the first time, NOA-04 confirmed the non-inferiority of CT as first-line treatment of all subtypes of AG.

In the RTOG 9402 trial, a total of 291 AO and AOA patients were randomly assigned to RT (59.4 Gy) alone (n = 148) or RT plus up to four cycles of intensified PCV (n = 143) administered before RT [9]. The primary endpoint was OS. No difference was observed in median OS for the entire cohort (HR: 0.79, p = 0.1) (Table 3). Patients with 1p19q codeleted AG had the longest survival (HR: 0.59, p = 0.03). In patients without 1p19q codeletion, OS was similar in both arms (HR: 0.85, p = 0.39) [9].

In the EORTC 26951 trial, a total of 368 newly diagnosed AO and AOA were randomly assigned to either RT (59.4 Gy) (n = 183) or RT (59.6 Gy) followed by up to six cycles of standard PCV (n = 185) starting 4 weeks at the conclusion of RT [10]. The co-primary endpoints were OS and PFS. After 140 months of follow-up, both median PFS and OS were significantly longer for the whole cohort in the RT + PCV arm (PFS: HR: 0.66, p = 0.003 and OS: HR: 0.75, p = 0.018) (Table 3). Similar to the RTOG 9402 trial, this improvement in survival was accounted for by the subset of 1p/19q codeleted tumors (PFS: HR: 0.42, p = 0.002 and OS: HR: 0.56, p = 0.059), whereas in non-codeleted tumors, only a non-significant trend toward improved PFS and OS was observed after RT + PCV (PFS: HR: 0.73, p = 0.026 and OS: HR: 0.83, p = 0.185). In this study, IDH mutation, 1p/19q codeletion and MGMT promoter methylation were prognostic, but not predictive [10].

NOA-04, RTOG 9402 and EORTC 26951 trials were designed using morphology-based analysis only. The NOA-04 trial confirmed the non-inferiority of CT as first-line of treatment of AG, including AA [11], whereas the RTOG 9402 and EORTC 26951 trials established RT + PCV as a new standard of care in 1p/19q codeleted AG [7,9,10]. The similar results in both RTOG and EORTC studies suggested that neither the timing (before or after RT) nor the dose intensity of the PCV schedule matters [10].

Questions that remain include the role of TMZ substituted for PCV CT in the adjuvant treatment of codeleted AG and the optimal the management of non-1p/19q codeleted tumors [7,10].

1p/19q codeleted AG: TMZ versus PCV

Only 46 and 30% of the patients completed the intended cycles of PCV CT in the RTOG and EORTC studies [9,10]. Both lomustine and procarbazine are responsible for cumulative myelotoxicity and procarbazine may cause allergic drug reactions and vincristine can result in a toxic peripheral neuropathy [11,17,18,20]. Other side effects of PCV that can impact receipt of treatment include treatment-associated fatigue, nausea and weight loss [84].

TMZ is widely considered as less toxic than PCV [10,11,18,44] and is thus substituted for PCV in many centers as confirmed in two survey studies [1,20,87,88]. A retrospective study of 1013 patients with AO/AOA suggested that PCV is more effective compared to TMZ with a longer median TTP [89]. Nevertheless, high response rates to TMZ with improved drug tolerance as compared to PCV have been reported in several small studies both in the first-line treatment and at recurrence in chemotherapy-naive patients (Table 4) [11,90–94]. The results of the NOA-04 trial did not reveal any difference in efficacy between TMZ and PCV CT, although no formal head to head comparison was performed or protocol specified [11]. In a subgroup of AG treated in the MRC (Medical Research Council) trial comparing PCV to standard dose and dose dense TMZ, no difference in response rate or survival was seen [94].

1p/19q codeleted AG: RT + TMZ

The role of RT plus concomitant and adjuvant TMZ in newly diagnosed AG has been evaluated only in four small retrospective studies, two with TMZ administered pre-RT followed by concomitant RT + TMZ [91,95] and two with concomitant RT + TMZ followed by up to 12 cycles of post-RT TMZ [96,97]. Two other series have reported on various combinations of RT and CT in AG (Table 5) [89,98].

The currently open and accruing randomized CODEL trial (comparing RT + PCV vs RT + TMZ) in patients with 1p19q codeleted AG will definitely answer whether TMZ may be substituted for PCV [16].

1p/19q codeleted AG: deferring RT

Improved median OS was observed in the EORTC 26951 and RTOG 9402 studies for patients with 1p/19q codeleted tumors treated with RT + PCV as stated above (median OS of 14.7 years in the RTOG study and median OS not reached after 12 years of follow-up in the EORTC study) [9,10]. Nonetheless, in patients with codeleted AG treated with RT + PCV, a significant risk of late neurotoxicity exists. After a mean follow-up of 12 years in patients free of tumor progression, a decline in attention and executive functions can be observed in patients treated with RT for WHO Grade II glioma whereas patients treated without RT maintained their baseline cognitive level [99]. More recently, cognitive function and health-related quality of life (HRQOL) were evaluated in a cohort of

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Table 4. Cohort and Phase II studies in newly diagnosed anaplastic glioma treated with Temozolomide.

Study (year)	Patients and tumor characteristics	Agent	Objective radiographic response rate	Median PFS	6-month PFS	Median OS	Ref.
Taliansky-Aronov 2006	20 patients with AO Median age: 47 years (26–65) Median KPS: 70% Resection: 9, Biopsy: 11 1p deletion: 58% (7/12), 19q deletion: 83% (10/12), 1p/19q codeletion: ND	TMZ 200 mg/m^2/d 5 d/28 up to 24 cycles # cycles: 14 (3–24)	PR: 15 (75%) SD: 2 (10%) PD: 3 (25%)	24 months	NR	NR	[90]
Mikkelsen *et al*. (2009) Description of the cases with CT	36 patients with 1p/19q codeletion Median age: 46.5 years (22–68) Median KPS 90 (60–100) Complete resection: 8 (22.2%), subtotal resection 22 (61.1%), biopsy: 6 (16.7%) AO: 5 patients (13.9%), AOA: 30 patients (83.3%), Anaplastic mixed: 1 pt (2.8%)	TMZ alone 150–200 mg/m^2/d 5 d/28 # cycles: 12 (2–24)	CR: 3 (8.6%) PR: 18 patients (51.4%) SD: 2 patients (20%) PD: 2 patients (20%)	28.7 months	94.3%	NR OS 12 mo: 97.2% OS 24: 90.1%	[91]
Gan *et al*. (2010)	40 patients Median age: 43 years (18–71) ECOG PS: 0 = 14 (35%); 1 = 23 (58%); 2 = 3 (7%) Complete resection: 9 patients (22%), subtotal resection: 27 patients (68%), Biopsy only: 4 patients (10%) 1p/19q codel: 47% (18/38) methylation MGMTp: 48% (10/21) AO n = 11 (1p/19q codel; 71%; MGMTp methyl 100%), AOA n = 29 (1p/19q codel: 31%; MGMTP methyl 23%)	TMZ 200 mg/m^2, 5d/28 up to 6 cycles (only 4 patients treated > 3 months)	CR: 15 patients (38%) PR: 6 patients (15%) SD: 9 patients (23%)	21 months	77%	43 months	[92]
Ducray *et al*. (2011)	41 patients Median age: 74 years (70–90) Median KPS: 60 (30 – 100) Complete resection: 2 patients (11%), partial resection: 9 patients (14%), biopsy: 33 patients (75%) MGMTp methylation: 50% (/38) 1p/19q codeletion: 7% (1/14)	TMZ alone 150 mg/m^2/d 5 d/28 # cycles: 5 (1–13)	PR: 13 patients (32%) SD: 17 patients (41%) PD: 11 patients (27%)	6.9 months	NR	12.4 months	[93]

AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; codel: codeletion; CR: Complete response; del: Deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; KPS: Karnofsky performance status; MGMTp: Methylguanine methyltransferase promoter; methyl: Methylation; MGMTP: O-6-methylguanine-DNA methyltransferase promoter; methyl: methylation; mo: Months; nb: Number; NR: Not reported; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival: PR: Partial response; RR: Response rate; SD: Stable disease; TMZ: Temozolomide; # cycles: Median number of cycles completed.

32 long-term survivors included in the EORTC 26951 trial [100]. Results were compared to healthy controls and to patients' own HRQOL 2.5 years after initial treatment. At the time of the study, median OS was 147 months and 27 patients had no recurrence of their disease. Of progression-free patients, 30% had severe cognitive impairment and 19% were not able to live independently. The HRQOL was worse compared to controls but similar to 2.5 years after initial treatment. In this study, no correlation was noted between cognition or HRQOL and the arm of initial treatment [100]. Considering these observations, many believe it is important to determine if RT can be safely deferred in patients with 1p/19q codeleted AG [16,20,87,88]. The POLCA trial, a French multicenter randomized Phase III trial, is designed to determine whether treating newly diagnosed 1p19q codeleted AG with PCV alone (and delay of RT until recurrence) versus RT + PCV can spare potential RT-related cognitive deterioration and achieve similar results with respect to PFS and OS. A trial initiated by the German NOA working group is to determine whether TMZ alone is superior to RT + PCV with respect to both OS and cognitive/functional outcome [20]. Notwithstanding CT alone has less cognitive impact compared to up-front RT, the benefit of CT only may be offset by early disease progression and associated functional/cognitive decline combined with the need for early salvage RT [20,101].

Table 5. Main cohorts and Phase II studies of newly diagnosed anaplastic glioma treated with radiotherapy and chemotherapy.

Study (year)	Patients and tumor characteristics	Agent	Objective radiographic RR	Median PFS	6-month PFS	Median OS	Ref.
Vogelbaum *et al.* (2009)	39 patients Median age: 45 (18–71), Zubrod PS = 0: 27 AO: 13 patients, AOA/oligo-dominant: 13 patients, AOA/oligoastro: 10 pt, AOA/astro-dominant: 1 pt, mixed glioma, not specified: 2 patients 1p/19q codeletion: 60.7% (23/36) MGMT methylation: 80% (16/20)	Pre-radiation TMZ (150 mg/m2/d, 7 on/off) × 6 cycles followed by RT (59.4 Gy) + concomitant TMZ (75 mg/m^2/d)	Pre-RT RR: 32% Pre-RT CR: 6% Pre-RT PR: 26% Pre-RT PD: 10%	NR PFS 30 months:64%	Only and 13 patients had progressed and 8 patients have died at the time of the analysis	NR OS 30 months: 81%	[95]
Mikkelsen *et al.* (2009) Description of the cases with CT + RT only	12 patients without 1p/19q codeletion Median age: 32 (18–81) Median KPS: 90 (60–100) Complete resection: 3 patients (25%), Subtotal resection: 8 patients (66.7%), Biopsy: 1 pt (8.3%) AO: 3 patients (25%), AOA: 9 patients (75%)	Pre-radiation TMZ (150–200 mg/m^2/d) × 2–4 cycles followed by chemoradiation (RT 60 Gy) + concomitant TMZ (75 mg/m^2/d)	NR	13.5 months	75%	NR OS 12 months: 83.3% OS 24 months: 83.3%	[91]
Kim *et al.* (2011)	33 patients Median age = 41 y (17–60), KPS ≥ 70: 88% >75% tumor resection: 58% AA: 21 patients (64%), AO: 12 patients (36%) 1p/19q codeletion: 53% (8/15) MGMTp methylation: 55% (11/20)	RT (59.4 Gy) + concomitant TMZ (75 mg/m^2, 7 d/week) followed by adjuvant TMZ (150 – 200 mg/m2 5 d/28) cycles	61%	Mean PFS: 48.7 months	NR	Mean OS: 66.4 months	[96]
Minniti *et al.* (2014)	84 patients Median age: 44y (22–67), Median KPS: 90 (60–100) Complete/subtotal resection: 47 patients (56%), Incomplete resection: 29 patients (33%), Biopsy: 8 patients (11%) AO: 59 patients (70%), AOA: 25 patients (30%) initial grade 2: 24 patients (28.5%) 1p/19q codel: 57% (48/84) IDH1 mutation: 63% (52/82) MGMT promoter methylation: 74% (57/77)	RT (59.4 Gy) + concomitant TMZ (75 mg/m^2 7 d/week) followed by adjuvant TMZ (150 – 200 mg/m^2 5 d every 28 d) (up to 12 cycles)	CR: 14% PR: 25% SD: 40%	45.2 months	NR	55.6 months	[97]

AA: Anaplastic astrocytoma; AO: Anaplastic glioma; AOA: Anaplastic oligoastrocytoma; codel: codeletion; CR: Complete response; CT: Chemotherapy; IDH: Isocitrate dehydrogenase; KPS: Karnofsky performance status; LGG: Low grade glioma; MGMTP: O-6-methylguanine-DNA methyltransferase; NR: Not reported; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PS: Performance status; RR: Response rate; RT: Radiotherapy; TMZ: Temozolomide; TTP: Time to progression.

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Table 5. Main cohorts and Phase II studies of newly diagnosed anaplastic glioma treated with radiotherapy and chemotherapy (cont.).

Study (year)	Patients and tumor characteristics	Agent	Objective radiographic RR	Median PFS	6-month PFS	Median OS	Ref.
Lassman *et al.* (2011) Description of the cases with CT + RT only	528 patients Median age: 43 y (20 – 83), KPS ≥ 70: 453 (86%) Resection: 466 (88%) AO: 262 patients (50%), AOA: 266 patients (50%), 1p19q codeletion: 40% (133/334)	CT + RT (n = 528) CT followed by RT (n = 132) RT+ concurrent CT (n = 112) RT followed by CT (n = 281) Doses not detailed	NR	4.1 years	NR	7.3 years	[89]
Shonka *et al.* (2013) Description of the cases with concomitant RT-CT only	52 patients AA Median age: 42 years (18–69), median KPS: 90 (60–100) Resection: 30 (63.8%), biopsy: 17 (36.2%), unknown: 5	RT (60 Gy) + Concurrent CT: BCNU: 3 (5.8%) TMZ: 49 (94.2%)	NR	1.5 years	NR	4.8 years	[98]

AA: Anaplastic astrocytoma; AO: Anaplastic glioma; AOA: Anaplastic oligoastrocytoma; codel: codeletion; CR: Complete response; CT: Chemotherapy; IDH: Isocitrate dehydrogenase; KPS: Karnofsky performance status; LGG: Low grade glioma; MGMTP: O-6-methylguanine-DNA methyltransferase; NR: Not reported; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PS: Performance status; RR: Response rate; RT: Radiotherapy; TMZ: Temozolomide; TTP: Time to progression.

Next trials in 1p/19q codeleted AG

CODEL trial

The Phase III CODEL trial [102] was initially designed to compare RT with concomitant and adjuvant TMZ, RT alone and TMZ alone in newly diagnosed 1p/19q codeleted AG. The trial was stopped after the long-term results of the RTOG 9402 and EORTC 26951 trials became available. The CODEL trial was subsequently amended and currently will compare three arms of treatment in 1p/19q codeleted gliomas (now including both WHO Grade II and III gliomas based on recent results of the RTOG 9802 trial) [7,20,103].These treatment arms include RT followed by PCV, RT with concurrent and adjuvant TMZ and TMZ alone (limited to 50 evaluable patients) to determine whether PFS and neurocognitive function (the study co-primary endpoints) differs between the three arms [7,20,103].

Uni- or non deleted tumors

The prognosis of uni- or non-codeleted AG is less favorable and their management remains controversial. Based upon the NOA-04, RTOG 9402 and EORTC 26951 trials, prospective data support management after initial surgery with either RT only or CT (TMZ or PCV) only [7,55]. The main controversy is whether these tumors should be treated similar to the current standard as for GB with RT and concomitant and adjuvant TMZ. A retrospective analysis of RTOG 9402 attempted to determine whether a subgroup of non-codeleted AG (32% of all patients in the study) benefit from combined chemo-RT [6]. The study posited that only IDH and ATRX mutated non-codeleted AG benefit from up-front RT + PCV CT (**Table 2**).

In the NOA-04 trial that included 59% of non1p19q codeleted AG, no difference was observed in time to disease progression according to the treatment allocation [11]. Moreover, both the RTOG 9402 and the EORTC 26951 trials have demonstrated the absence of benefit in non-codeleted population with the addition of PCV to RT as compared to RT only (except possibly in the IDH and ATRX mutated subgroup as stated) [9,10]. In a retrospective cohort of 163 AA, 31% were treated by concurrent chemoradiation (TMZ in 94.2%), 26% received RT alone, 38% RT followed by CT and 3% by CT alone. Median PFS was superior in the RT alone arm (not reached after a median follow-up of 4.2 years) compared to concurrent chemoradiation (1.5 years) and RT followed by CT (3.6 years). Median OS was 5.7 years and did not significantly differ between arms. The rate of radionecrosis was higher in instances of concurrent chemoradiation (11.5%) or RT followed by CT (7.9%) as compared to RT alone (2.3%). These data support RT alone in AA patients as initial treatment [98]. The National Comprehensive Cancer Network (NCCN) recommends treatment of newly diagnosed AA by RT only followed by observation and chemotherapy at progression [76]. In summary, combined radiochemotherapy has not been established as superior to RT only or CT only in newly diagnosed non-codeleted AG [20,55,76,104].

The open and accruing randomized four-arm CATNON Phase III trial [105] in newly diagnosed non-codeleted AG will determine whether combined RT and TMZ (as concomitant

plus adjuvant or as adjuvant treatment) is superior to RT alone. Non-codeleted patients are randomized between RT with or without concomitant TMZ, and after RT, a second randomization allocates patients to adjuvant TMZ (12 cycles) or not.

Management of newly diagnosed AG

The management of AG increasingly is based on the molecular classification (Figure 1) [20]. By way of example, IDH mutated/ G-CIMP-positive, 1p/19q codeleted AG have several therapeutic options varying in evidence-based recommendations. Therapeutic options include enrollment in the CODEL trial, RT and adjuvant PCV (considered the current standard of care based on the RTOG and EORTC trials), RT and adjuvant TMZ (one of four arms in the CODEL trial for which currently there is very limited data), RT plus concomitant and adjuvant TMZ (again one of four arms of the CODEL trial and for which there is limited data) or CT only (TMZ or PCV; based on results of the NOA-04 trial). Figure 1 illustrates various treatments for the currently recognized molecular subtypes of AG; however importantly these treatment options often lack prospective supporting data. Notwithstanding lack of prospective data as stated, there are many that consider RT plus concomitant and adjuvant TMZ as a primary treatment choice for all newly diagnosed AG and hence its inclusion as a treatment option for all molecular subtypes of AG.

Recurrent disease

No standard therapy has been established for recurrent AG (Table 6). At progression, therapeutic options depend on initial treatment as well as clinical characteristics (age and performance status), radiographic imaging data, response to initial treatment and time between initial treatment and progression [106].

A second surgery can be offered when a re-resection is feasible and of potential clinical benefit, notwithstanding only limited data supporting this recommendation [106,107]. Implantation of carmustine wafers at time of re-resection can as well be considered [7,21,108].

RT is indicated in recurrent AG not previously irradiated as demonstrated in the NOA-04 trial. Re-irradiation may also be considered in select patients with small volume recurrences previously treated by RT, although limited data are available supporting this recommendation [1,7,55,109,110]. Several RT techniques are used for re-irradiation including single or fractionated stereotactic RT, conformal RT or image-guided RT [7].

Given the limited application of repeat surgery and re-radiation, systemic therapies represent the main treatment approach for recurrent AG. In patients not previously treated with CT, alkylating CT is the treatment of choice [7]. The efficacy of TMZ and nitrosoureas appears similar consequently a nitrosourea CT is often administered after progression on TMZ [7,94].

In the NOA-04 trial, patients initially treated with CT received RT at first progression and patients initially treated with RT received either TMZ or PCV at first progression [11]. In the RTOG 9402 and EORTC 26951 trials, various CT regimens depending upon initial treatment were used [9,10]. Rechallenge with TMZ, lomustine or PCV or bevacizumab all represent therapeutic options (Table 6). Response rates are usually lower and duration of response are relatively limited in recurrent AG treated with CT [55,103].

Studies in recurrent AA reported objective radiographic response rates ranged from 7% to 35% and median PFS ranging from 2.75 to 11.5 months (Table 6) [55,108,111–126]. A Phase II trial evaluated the efficacy of TMZ in first- and second-line CT in 162 patients, most with AA. A response rate of 35% was reported in patients naive to CT and 20% for patients previously treated with a nitrosourea [110]. These results led to the accelerated approval for TMZ for recurrent AA by the US Food and Drug Administration. Similar (22.5 and 26%) or higher (44%) responses rates were observed in other cohort studies [127–129]. In a recent retrospective case series of 35 patients with recurrent AA previously treated by surgery, RT and TMZ, partial response was observed in 5.7% and stable disease in 54% treated with lomustine. The median PFS and OS was 4.5 and 9.5 months respectively after lomustine onset [55].

Response rates ranging between 50 and 70% in recurrent AO are reported when treated with alkylating chemotherapy [81,84,85,90]. Response rates ranging from 42 to 73% have been observed with either PCV or TMZ in recurrent AO [81,83–85,129,130]. The role of TMZ in recurrent AO and AOA after prior PCV and RT was investigated in the EORTC 26972 Phase II trial. In patients with AO (n = 32), the response rate was 25% and the median TTP for responding patents was 8.0 months [131].

No difference in efficacy between TMZ and PCV was seen when given at first recurrence following initial surgery and RT only in recurrent AG [94]. Data on other treatment regimens such as cisplatin/etoposide, paclitaxel, irinotecan, cyclophosphamide and carboplatin are limited.

The results of these differing studies are difficult to compare, as treatment after progression is affected by the initial treatment and the response to first-line treatment which differ significantly between studies [7,84]. Moreover, the molecular classification and often the WHO classification are also inhomogeneous in these various and differing studies.

Although not approved for recurrent AG, bevacizumab, alone or in combination, represents another option after failure of RT and alkylating agents or because of intolerance to CT [7,55,100,132–136]. Available data are mainly derived from retrospective studies in AG (Table 6) [132–135,137–147]. In these studies, the response rates ranged between 15 and 79%, median PFS between 5.0 and 13.4 months and median OS between 6.8 and 12.6 months. A prospective Phase II trial evaluated the efficacy of bevacizumab as single agent in 31 patients with recurrent AG. Patients had received a median of 2 (range, 0–7) prior CT regimens before the initiation of bevacizumab. Partial responses were observed in 43%, median PFS was 2.93 months and median OS was 12 months [144]. These results are remarkably similar to historical controls treated with non-bevacizumab therapies however (median PFS varied from 2 to 6 months and median OS from 9 to 11.8 months) [114,115]. The currently open and accruing EORTC 26091 randomized trial, TAVAREC [148], will determine whether TMZ is more effective

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Table 6. Treatment overview of recurrent anaplastic glioma.

Study (year)	Patient number	Prior chemotherapy	Agent	Objective radiographic response rate	Median PFS (months)	6-month PFS	Median overall survival (months)	Ref.
Brada (MRC trial)	447 (51 AA)	None (RT only)	PCV (n = 224) or standard (n = 112) or dose dense TMZ (n = 111)	NR	PCV: 3.6 sd TMZ: 5.0 dd TMZ: 4.2	PCV: 34.5% sd TMZ: 46.9% dd TMZ: 36.2%	PCV: 6.7 sd TMZ: 8.5 dd TMZ: 6.6	[94]
Wick	73	None (RT only)	PCV (n = 32), TMZ (n = 41)	NR	12.6	NR	NR	[11]
Levin *et al.* (1992)	44 (38 AA)	CCNU, PCV, CBDCA (79%)	Diflornithine (DFMO)	9%	4.2	36%	NR	[119]
Levin *et al.* (1992)	38	BCNU/CCNU (50%)	TPDC-FUHU	34%	11.5	70%	NR	[118]
Brem *et al.* (1995)	28	None	BCNU wafers	NR	NR	64%	12	[108]
Yung *et al.* (1996)	28 (15 AA)	CCNU/BCNU (100%)	cis-retinoic acid	11%	3.75	35%	11.75	[116]
Kyritsis *et al.* (1996)	47	CCNU/BCNU/procarbazine (36%)	TPCH	23%	5.8	30%	NR	[126]
Yung *et al.* (1996)	162 (AA + AOA)	CCNU/BCNU (60%)	TMZ	35%	5.4	46%	13.6	[116]
Wong *et al.* (1999)	150	CBDCA/cis-retinoic acid/ procarbazine/alpha-interferon/DFMO (77%)	Composite of 8 Phase II trials	14%	3.25	31%	7.5	[114]
Kunschner *et al.* (1999)	19	BCNU/CCNU (100%)	Carboplatin, VP16	5%	2	12%	NR	[120]
Chamberlain *et al.* (1999)	20	BCNU/CCNU (100%)	Placlitaxel	13%	6	40%	18.5	[122]
Hess *et al.* (1999)	150	CBDCA/cis-retinoic acid/ procarbazine/alpha-interferon (66%)	Composite of 8 Phase II trials	9.1%	NR	36%	NR	[123]
Jaeckle *et al.* (2003)	48 (35 AA)	CCNU/BCNU/TMZ (78%)	cis-retinoic acid + TMZ	10.7%	6	50%	10.8	[117]
Desjardins *et al.* (2007)	39 (32 AA)	TMZ (100%)	HU, imatinib	10%	2.75	24%	7.5	[124]
Chamberlain *et al.* (2006)	40	TMZ (100%)	Cyclophosphamide	22.5%	4	30%	8	[113]
Chamberlain *et al.* (2008)	40	TMZ (75%); BCNU (25%)	CPT11	23%	4.1	40%	6.9	[112]

6TG: 6-thiogunaine; AA: Anaplastic astrocytoma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligodendroglioma; BCNU: Carmustine; CCNU: Lomustine; CPT11: Irinotecan; CT: Chemotherapy; dd TMZ: Dose dense temozolomide; DFMO: Diflornithine; HU: Hydroxyurea; NR: Not reported; PCV: Procarbazine, lomustine, vincristine; PFS: Progression-free survival; sd TMZ: Standard temozolomide; TMZ: Temozolomide; TPCH: 6-thioguanine, procarbazine, CCNU, hydroxyurea; VP16: Etoposide.

Table 6. Treatment overview of recurrent anaplastic glioma (cont.).

Study (year)	Patient number	Prior chemotherapy	Agent	Objective radiographic response rate	Median PFS (months)	6-month PFS	Median overall survival (months)	Ref.
Lamborn *et al.* (2008)	159	BCNU/CCNU (51%)	Composite of 12 Phase II trials	7%	3.75	28%	8	[115]
Walbert *et al.* (2011)	31	TMZ (80%)/CCNU (20%)	6TG, TMZ/CCNU, capecitabine, celecoxib (TCCC)	26%	5.8	48%	13.5	[121]
Franceschi *et al.* (2012)	128 (66 AA)	TMZ (50%), PCV (10%)	TMZ (75%), PCV (9%), other (16%)	NR	7.1	57.8%	18.3	[125]
Chamberlain *et al.* (2015)	35	TMZ (100%)	CCNU	5.7%	4.5	40%	9.5	[55]
Desjardins *et al.* (2008)	33 (25 AA)	TMZ (100%)	Bevacizumab + irinotecan	61%	7.5	55%	16	[132]
Norden *et al.* (2008)	21	TMZ (100%)	Bevacizumab	34%	5.8	32%	NR	[137]
Chamberlain *et al.* (2009)	31 (31 AA)	TMZ (100%)	Bevacizumab	64%	7	60%	9	[138]
Chamberlain Johnston Cancer *et al.* (2009)	22 (22 AO)	Alkalyting agents, heavily pretreated	Bevacizumab	64%	8	68%	9	[132]
Reardon *et al.* (2009)	32 (13 AA)	TMZ (100%)	Bevacizumab + VP16	24%	6	41%	15.7	[139]
Zuniga *et al.* (2009)	14 AG	Various CT, including Irinotecan, antiangiogenic treatments	Bevacizumab + irinotecan	78.5%	13.4	78.6%	Not reached	[140]
Poulsen *et al.* (2009)	47	At least 2 CT regimens (TMZ, PCV, omatinib + hydroxycarbamide)	Bevacizumab + irinotecan	25%	5.5	32%	8	[141]
Taillibert *et al.* (2009)	25 (AO/AOA)	TMZ, nitrosoureas (up to 4 previous CT)	Bevacizumab + irinotecan	72%	4.6	42%	NR	[135]
Sathornsumetee *et al.* (2010)	32 (24 AA)	TMZ (94%)	Bevacizumab + erlotinib	31%	5.4	44%	17.7	[142]
Kreisl *et al.* (2011)	31 (21)	TMZ (100%)	Bevacizumab	43%	2.9	20.9%	12	[144]

6TG: 6-thiogunaine; AA: Anaplastic astrocytoma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligodendroglioma; BCNU: Carmustine; CCNU: Lomustine; CPT11: Irinotecan; CT: Chemotherapy; dd TMZ: Dose dense temozolomide; DFMO: Diflornithine; HU: Hydroxyurea; NR: Not reported; PCV: Procarbazine, lomustine, vincristine; PFS: Progression-free survival; sd TMZ: Standard temozolomide; TMZ: Temozolomide; TPCH: 6-thioguanine, procarbazine, CCNU, hydroxyurea; VP16: Etoposide.

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Table 6. Treatment overview of recurrent anaplastic glioma (cont.).

Study (year)	Patient number	Prior chemotherapy	Agent	Objective radiographic response rate	Median PFS (months)	6-month PFS	Median overall survival (months)	Ref.
Hofer *et al.* (2011)	49	NR	Bevacizumab + various CT	NR	NR	NR	9.1	[143]
Moller *et al.* (2012)	33	Alkylating agents	Bevacizumab + irinotecan	21%	3.7	30%	6.9	[146]
Gil *et al.* (2012)	36	TMZ	Bevacizumab + irinotecan		4.6	43%	11.2	[145]
Seystahl *et al.* (2012)	39 (6 AA)	TMZ (100%)	Bevacizumab alone or + irinotecan	26%/33%	4.2/4.7	29%/42%	14.8/8.1	[133]
Delios *et al.* (2012)	39 (26 AA)	TMZ (100%)	Bevacizumab alone or in combination	41%	5	NR	11	[147]

6TG: 6-thiogunaine; AA: Anaplastic astrocytoma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligodendroglioma; BCNU: Carmustine; CCNU: Lomustine; CPT11: Irinotecan; CT: Chemotherapy; dd TMZ: Dose dense temozolomide; DFMO: Difluornithine; HU: Hydroxyurea; NR: Not reported; PCV: Procarbazine, lomustine, vincristine; PFS: Progression-free survival; sd TMZ: Standard temozolomide; TMZ: Temozolomide; TPCH: 6-thioguanine, procarbazine, CCNU, hydroxyurea; VP16: Etoposide.

when given with or without bevacizumab at first recurrence in tumors that demonstrate contrast enhancement by MRI in patients with either WHO Grade II or III non-codeleted gliomas.

After failure of bevacizumab, a recent meta-analysis did not demonstrate significant differences in OS between bevacizumab containing or non-bevacizumab containing salvage therapies [149]. Another retrospective study suggested an improved survival when bevacizumab was continued post-bevacizumab progression [133]. Currently, there is no evidence-based recommendation regarding management of patients progressing on bevacizumab, an unmet need in neuro-oncology.

Expert commentary

The current WHO 2007 pathology classification of AG is prone to high inter-observator discordance. This classification will be improved by incorporation of molecular markers that will not only provide greater precision in diagnosis and prognostication but in addition define subgroups of AG and their treatment. By example, patients with G-CIMP positive tumors and 1p/19q codeletion have the best prognosis, followed by patients with G-CIMP-positive tumors and non-1p/19q codeletion. Patients with G-CIMP negative tumors and non-deleted had the worst prognosis and could be considered as GB-like.

The current standard of care in 1p/19q codeleted AG established by the RTOG 94–02 and the EORTC 26951 trials consists of RT followed or preceded by PCV. TMZ is widely recognized as less toxic and is often substituted for PCV. The currently open and accruing randomized CODEL (in codeleted tumors) and CATNON (in non-codeleted tumors) trials will definitely determine whether TMZ may be substituted for PCV and define the new standard of care for non-codeleted AG. The possibility of deferring RT in the initial treatment of 1p19q codeleted AG will also be determined in the French POLCA and German NOA trials.

Treatment of recurrent AG is not standardized and currently depends on patient and tumor characteristics as well as the initial treatment. New compounds and immunological approaches targeting mutations in IDH, EGFRvIII, BRAF and MET are current research efforts and may provide new therapeutic options in recurrent AG.

Five-year view

The molecular categorization of AG will improve diagnosis and provide both prognostic as well as predictive value to currently utilized morphology-based pathology [65]. For example, the role of molecular classification of AG based on large-scale genomic or epigenomic analyses was recently demonstrated in a cohort of cohort of 228 patients with AG [65]. Illumina Infinum Human Methylation 450 Bead Chip arrays (HM450) were employed to define genome-wide methylation profiles and DNA copy number changes. Algorithms were developed that combine G-CIMP and IDH mutation, 1p/19q codeletion and MGMT promoter methylation using the HM450 single assay. A 92% concordance for IDH1 mutation and 1p/19q

codeletion status was obtained. When the samples were discordant, survival analyses suggested an improved assessment of biological phenotype by the HM450 analysis when compared to traditional immunohistochemistry. Genomic profiling is, therefore, likely not only to improve the diagnosis of AG and guide management, but also will likely identify novel therapeutic targets [103]. Several molecular alterations, including mutations in IDH, EGFR, BRAF and MET have been identified as potential therapeutic targets [35,150]. Two compounds targeting mutant IDH1 R132H (AGI 5198 or Dacogen) and IDH2 R140Q (AGI 6780) have been developed [52–54] and first in human studies in glioma are ongoing.

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Key issues

- Anaplastic glioma (AG) represent 6–15% of all newly diagnosed of primary brain tumors [1,2].
- The WHO 2007 classification is prone to high interobservator discordance between the three morphology-based groups of AG [7,24–27].
- Molecular biomarkers add diagnostic, prognostic and predictive value to the current morphological classification of AG and increasingly influence treatment. Recognized as useful in the management of AG are the molecular biomarkers of IDH mutation, 1p/19q codeletion, MGMT promoter methylation and ATRX mutation.
- AG can be robustly divided into three main molecular groups based on genome wide DNA methylation and copy-number alterations independent of histology: G-CIMP-negative tumors, which molecularly resemble GB, G-CIMP-negative, non-codeleted tumors and G-CIMP-positive, codeleted tumors [25].
- The NOA-04 trial confirmed the non-inferiority of alkylator-based CT versus RT only as first-line treatment of AG [11].
- The RTOG 9402 and EORTC 26951 trials established RT + PCV as the standard of care in 1p/19q codeleted AG [7,9,10].
- Uni- or non-codeleted AG based on the NOA-04 trial are treated with RT only followed by observation and chemotherapy at progression. Alternatively, these tumors may be treated with alkylator-based chemotherapy only followed by observation and RT only at progression [82]. Combined chemoradiotherapy is currently not established as the standard of care for non-codeleted tumors [20,56,82,111].
- The risk of RT-associated neurotoxicity, in particular cognitive impairment, remains a challenge particularly in the 1p9qcodeleted subset of AG due in part to long survival. The mature results of NOA-04 and the results of CODEL and CATNON trials will further determine the best up-front treatment strategy in AG.
- Although not approved for recurrent AG, bevacizumab, alone, represents a therapeutic option after failure of RT and alkylating CT or because of intolerance to chemotherapy [7,56,110,138–142].

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