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The impact of concurrent temozolomide with adjuvant radiation and IDH mutation status among patients with anaplastic astrocytoma

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Abstract

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This study assesses the controversial role of temozolomide (TMZ) concurrent with adjuvant radiation (RT) in patients with anaplastic astrocytoma (AA). The impact of isocitrate dehydrogenase (IDH) status on therapy and outcomes is also examined. All adult patients diagnosed with AA from 2001 to 2011 and treated with standard doses of adjuvant RT were identified retrospectively for clinical data extraction. IDH status was determined by IDH1-R132H immunostain and sequencing for other mutations in IDH1/IDH2. Cumulative survival probabilities were estimated using the Kaplan-Meier method. Cox proportional hazards regression models were fit for univariable/multivariable analyses. 136 patients had received concurrent TMZ while 29 had not. Of these, IDH status was determined on 114 and 27 patients, respectively. On univariable analysis, improved five-year survival was independently associated with concurrent TMZ (46.2 vs. 29.3 %, $p = 0.02$) and IDH mutation (78.9 vs. 22.0 %, $p < 0.001$). IDH mutation was additionally associated with a greater likelihood of extensive resection possibly secondary to a more favorable tumor location. Gross total/subtotal resections also led to improved survival when compared to biopsy alone on univariable analysis. On multivariable analysis, the association with five-year survival persisted for both concurrent TMZ and IDH mutation, but not with extent of surgery. Both IDH mutation and concurrent TMZ are associated with improved five-year survival in patients with AA who are receiving adjuvant RT. Secondly, the association between five-year survival and extent of resection is lost on multivariable analysis. This suggests a possible association between IDH mutation, tumor location and consequent resectability.

Keywords

Anaplastic astrocytoma; Temozolomide; Isocitrate dehydrogenase mutation; Malignant glioma

Introduction

Anaplastic astrocytomas (AA) are diffusely infiltrative astrocytic tumors with cellular anaplasia and mitotic activity but, unlike glioblastoma (GBM), they have neither microvascular proliferation nor necrosis [1]. Although less aggressive than GBM, mortality is still quite high with a five-year survival rate of only 25.9 % [2]. The prognostic role of isocitrate dehydrogenase (IDH) mutations in gliomas has recently been gaining significant attention [3–6]. In Yan's landmark study [4], patients with IDH mutated AAs had longer survivals than those with IDH wild-type tumors (median survival 65 vs. 20 months, $p < 0.001$). In fact, IDH wild-type AAs have a worse prognosis than IDH-mutated GBM [7], bringing the current classification of gliomas into question.

The role of adjuvant radiation therapy (RT) is well established in AA [8]; however the use of chemotherapy is more debatable [9–14]. After the advent of temozolomide (TMZ) concurrent with RT in patients with GBM [15], extrapolation of this regimen to patients with AA has been considered an acceptable alternative to RT alone [16] given the known activity of TMZ in this disease [17, 18]. Although clinical trials are underway to examine the role of TMZ concurrent with RT (RT+TMZ) in AA [19], the current dearth of published data supporting such an extrapolation has led to continuing disagreement.

This study was designed to assess whether RT–TMZ in a retrospective cohort of patients with AA is associated with an improvement in overall survival compared to RT alone. Furthermore, this study aimed to examine the influence of IDH status in this relationship.

Materials and methods

A cohort of all adult patients diagnosed with AA from 2001 to 2011 according to the WHO classification of brain tumors (2007) [1] and treated with standard doses of adjuvant RT was identified retrospectively using the neurooncology database at the Mayo Clinic (Rochester, MN). Pathology was re-reviewed for this study to confirm the diagnosis. Tumors with oligodendroglial components were excluded. Patient clinical data were extracted from the electronic medical record. Pre-operative MRIs were re-reviewed to confirm tumor size and location. Postoperative MRIs were also re-reviewed to determine the extent of resection. Assessment of extent of resection was based on removal of contrast enhancing disease on T1-weighted imaging. IDH mutation status was assessed on all available patient tumors by obtaining IDH-1-R132H immunostain on existing unstained slides or paraffin block sections (see supplementary figure 1). All specimens determined to be IDH1 wild-type by immunostain were also assessed for IDH mutations by pyrosequencing whenever sufficient tissue was available. A subset of the cases with IDH132H mutation by immunostain was confirmed by pyrosequencing to confirm internal validity (n = 17). 1p/19q testing was not conducted as only pure AAs were evaluated in this sample. Determination of MGMT promoter methylation status was considered however insufficient tissue prohibited assessment on many tumor samples.

The primary endpoint for the study was overall survival. Event-free survival (EFS) was also assessed and was defined as the time between diagnosis and either disease progression or death. The date of progression was based on the treating clinician's judgment as documented in the medical record. This avoids the complications and bias that would result from making retrospective assessments of pseudoprogression based on radiologic imaging and awareness of eventual outcome.

Patients who did/did not receive RT–TMZ were compared with regards to demographic and baseline clinical variables. Although descriptive information concerning general performance status and neurologic status were available, we elected not to classify patients by Karnofsky performance status or neurologic function status retrospectively, owing to the questionable validity of such an approach. Categorical variables were presented as counts and frequencies. Continuous variables were presented as means and standard deviations. Group comparisons were made using the Chi square test, Fisher's exact test or two-sample *t* test as appropriate. Cumulative survival probabilities were estimated using the Kaplan-Meier method. Univariable and multivariable Cox proportional hazards regression models were fit to compare patient groups. The fit of the proportional hazards model was tested and satisfied for models assessing five-year survival and five-year-EFS but not for those assessing overall survival and EFS. Hence, all models developed involved the former outcome variables. All analyses were conducted using SAS statistical software v. 9.3 (SAS Institute Inc., Cary, NC). In all cases, two-sided *p* values of <0.05 were considered statistically significant.

The study was approved by the Mayo Clinic Institutional Review Board.

Results

218 patients with AA were identified. 53 patients were excluded from this database (see Fig. 1). The remaining 165 patients (76 % of the original pool) were further assessed. The median duration of follow up for surviving patients ($n = 89$) was 36.4 months. 136 patients had received RT–TMZ while 29 had received RT alone (without concurrent TMZ). The median dose of RT was 59.4 Gy (range 40–64.8 Gy) in 33 fractions (range 15–36). All patients included in the RT–TMZ cohort were treated with a standard dose of 75 mg/m²/day of TMZ during the period of RT. The median number of cycles of adjuvant TMZ administered after completion of RT was six (range 0–43) in the RT–TMZ cohort and zero (range 0–8) in the RT cohort. In the RT cohort, three patients received adjuvant TMZ after completion of RT and nine patients received TMZ at a later stage during the course of their disease. Due to the dependency of the administration of adjuvant/palliative TMZ on the receipt of concurrent TMZ and the wide range in the number of cycles of TMZ administered after either RT–TMZ or RT in this study, adjuvant TMZ after RT and palliative TMZ at recurrence could not be reliably assessed as independent variables in multivariable analysis.

141 (85 %) had sufficient tissue to permit evaluation for IDH status (see supplementary figure 1). 60 patients were IDH mutated (IDH1-R132H = 51, IDH1-R132C = 4, IDH1-R132G = 3, IDH1-R132S = 1, IDH2-R172 K = 1).

Three patients did not have complete radiology images available and hence tumor size and location could not be confirmed. These patients were included in the overall survival analyses but were excluded from event-free survival analyses.

An expected difference was noted between treatment groups in the receipt of adjuvant TMZ after the completion of RT (see Table 1). Patients who received RT–TMZ were far more likely to receive further adjuvant TMZ than those in the RT cohort. Another expected difference was observed in the year of diagnosis. Prior to the advent of RT–TMZ for GBM (2001–2003) [15], all patients in this study ($n = 19$) were treated with RT without TMZ. From 2004 onwards, only 10 patients received RT without TMZ (five patients received adjuvant therapy at other institutions, two elderly patients received shortened courses of RT (40 Gy in 15 fractions), two patients opted against receiving TMZ and one patient was not offered TMZ by the treating physician despite optimal performance status). No other variables were statistically dissimilar between the two cohorts.

Patients with IDH mutated tumors were younger than their wild-type counterparts (see Table 1). IDH mutated tumors were more frequently localized to the frontal lobe (55.2 %) in comparison to IDH wild-type tumors (23.5 %). All AAs in the ‘other location’ category (e.g. thalamus, basal ganglia) were IDH wild-type ($n = 9$). IDH wild-type tumors were also smaller and more likely to have undergone a biopsy alone without a resection.

For further analysis, patients who underwent gross total resection and subtotal resection were grouped together as their survival curves were similar, yet quite different from those of patients who underwent biopsy alone (see supplementary figure 2). Similarly, the survival

curves of patients with tumors in the frontal, parietal and occipital lobes were similar enough to be grouped together, while those in other areas (temporal, brainstem, other) were also grouped together (see supplementary figure 3).

Univariable analysis revealed that RT–TMZ was associated with improved survival when compared to RT alone (53.1 months vs. 31.4 months, $p = 0.02$) (see Fig. 2 and Table 2). The five-year survival was 46.2 versus 29.3 %, respectively. More impressively, IDH mutation was associated with a dramatic improvement in survival when compared to the IDH wild-type AAs (five-year survival: 78.9 vs. 22.0 %). When stratified by both IDH status and TMZ receipt, statistical analyses were underpowered to draw meaningful conclusions. Patients with IDH mutations seemed to fare better than those with IDH wild-type tumors, regardless of the treatment received (see supplementary figure 4 and supplementary table 1). A trend towards improvement in five-year survival with the administration of TMZ was also noted in both groups; however this relationship was not significant. Other variables that portended an improved survival on univariable analysis included a younger age, a more extensive resection, tumor location (frontal, parietal or occipital) and a larger tumor size.

On multivariable analysis, RT–TMZ, IDH mutation and younger age continued to demonstrate a favorable survival outcome (see Table 3). Tumor location, size and unexpectedly the extent of resection was not associated with survival.

Univariable and multivariable analyses of event-free survival were also assessed and demonstrated very similar results (see supplementary figures 5, 6 and 7; supplementary table 2).

Discussion

Given the current absence of guidance based on randomized controlled clinical trials, the favorable association between survival and RT–TMZ among patients with AA is an important finding in this study. However, interpretation of these results must be made with caution due to the possibility of selection bias. First of all, this study is based on a retrospective, single-institution cohort. Most patients with AA at our institution are treated with RT–TMZ. A careful review of the clinical records of all patients in the RT cohort revealed that only two of these patients did not receive TMZ due to their advanced age. The decision to administer RT without TMZ on all other patients was not based on performance status or any other baseline variables. Univariable analyses did reveal a non-significant trend towards more favorable characteristics among those receiving RT–TMZ (younger age, more extensive resection and a larger proportion of IDH mutations). Nevertheless, multivariable analyses supported the survival advantage with RT–TMZ, even after controlling for multiple possible confounders. The absence of reliable performance status data due to incomplete documentation prevented formal multivariable evaluation of this variable. Hence, although performance status did not significantly influence the decision to administer TMZ, this study was unable to confirm that this did not impact the survival analyses.

Most of the patients who received RT received treatment in the years 2001–2003 while all of the patients who were treated with RT–TMZ were treated from 2004 onwards. This leads to

concern on whether the beneficial effect of TMZ may be confounded by other advances in medicine which may have arisen over time. However, multivariable analysis did not indicate this variable to be a confounder. The RT cohort was also separately evaluated by dividing it into two groups—patients treated before the advent of RT+ TMZ in GBM (i.e. 2001–2003) and patients treated after this period (i.e. 2004–2011). Survival analyses of these two cohorts did not reveal any significant differences in five-year survival (31.6 vs. 24.0 %, $p = 0.67$; see supplementary figure 8). These evaluations reduce the likelihood for any significant bias arising from the year of diagnosis in this study.

The study more clearly supports the improved outcome of patients with IDH mutations. The five-year survivals of IDH mutant and IDH wild-type AAs were 78.9 and 22.0 % respectively. The median overall survivals for these groups were 111.7 and 20.0 months respectively. The former value may be an overestimation secondary to the limited long-term follow up of surviving patients (median = 36.4 months). This also explains why the proportional hazards assumption was satisfied for five-year survival models rather than for overall survival models. Nevertheless, the prognostic ability of IDH status to independently differentiate between a five-year survival of 22.0 % in IDH wild-type tumors and 78.9 % in IDH mutated tumors remains quite remarkable. These results suggest that IDH testing should be considered in all patients with AA as it may impact patient counseling on prognosis.

Two other recent retrospective analyses in patients with AA did not find a survival benefit with RT+TMZ [20, 21]; however IDH status was not addressed in either of these studies. Central pathologic review was also not performed in one of these studies [20]. The older median age in that study (55 years) along with the poorer median overall survival (20.6 months) is suggestive of a higher proportion of IDH wild-type gliomas, many of which may have actually been misdiagnosed glioblastomas. In the second study [21], central pathologic review was performed, however the median overall survival of patients who received RT alone was unusually high compared to other published experiences of patients with AA [14, 22]. This suggests a possible excess of IDH mutated AAs. Such imbalances between the treatment groups in the distribution of patients with IDH mutations may have accounted for the absence of survival benefit with TMZ in these studies.

All pathology specimens in this study were re-reviewed; however 58.0 % of the IDH wild-type tumors in our study underwent biopsy alone as opposed to 18.3 % of the IDH mutant tumors. Hence, part of the poorer outcomes of IDH wild-type AAs may potentially be attributable to a larger proportion of misclassified GBMs in this cohort. Sampling bias is inevitable in both prospective and retrospective studies when resection is not feasible [23]. Omitting patients who cannot be resected introduces other biases. Insufficient tissue also prevented sequencing in 51 of the 81 IDH wild-type tumors (by immunostain). So, it is possible that a proportion of these may have had other IDH mutations. That being said, a comparison of the survival curves generated in this study with those in Yan's [4] reveals that the median survival in the IDH wild-type AA cohort (20 months) is identical to that described in our study. This similarity reduces the likelihood that misclassification is a significant issue.

Glioma-CpG island methylator phenotype (G-CIMP) is highly correlated with IDH mutation [24], so it is likely that most patient tumors with an IDH mutation also demonstrated MGMT promoter hypermethylation. However, MGMT promoter methylation has recently been demonstrated to be prognostic for overall survival in AA, independent of IDH status [25]. Furthermore, MGMT promoter methylation may also predict response to TMZ in IDH wild-type gliomas [26]. Evaluation for MGMT promoter methylation status was considered to add to the robustness of the multivariable analysis; however the lack of sufficient tissue in many patients would have sharply reduced the number of patients with complete data. The resulting diminished sample size would have prevented any meaningful statistical analysis.

The proportion of IDH mutated AAs in this study (43 %) is lower than that observed in other studies [4, 7]. As glioblastomas are typically IDH wild-type and are known to benefit from RT-TMZ, it is possible that the excess of patients with IDH wild-type AA in this study may have exaggerated the benefit of RT-TMZ. Stratification by both IDH status and TMZ was attempted. However this study was not powered sufficiently to discern the predictive value of IDH status with regards to benefit from treatment. A trend towards improved five-year survival among patients treated with RT-TMZ was noted regardless of the IDH status; however the majority of the difference between the survival distributions is attributable primarily to IDH status rather than chemotherapy receipt.

Another unexpected but interesting finding in this study was the lack of association between the extent of surgery and survival on multivariable analysis. Prior studies have demonstrated that outcomes improve with a more extensive resection of AAs [27, 28]. Further investigation into this matter revealed certain relationships between IDH status and tumor location. IDH mutant tumors were significantly more likely to be localized to the frontal, parietal or occipital lobes of the brain (70.7 % of IDH mutant AAs vs. 39.5 % of IDH wild-type AAs, $p < 0.001$) while IDH wildtype tumors were more likely to be localized to the temporal lobe (13.8 % of IDH mutant AAs vs. 33.3 % of IDH wild-type AAs). Furthermore, of the 9 patients in the 'other tumor location' category (8 localized to the thalamus and 1 in the basal ganglia), none of these were IDH mutant. Interestingly, when the data from the excluded patients with brainstem AAs ($n = 6$) and spinal cord AAs ($n = 1$) were analyzed, these too were all found to be IDH wild-type. Another association was that IDH mutant tumors were also more likely to have undergone a resection (either gross total or subtotal) rather than biopsy alone (81.7 vs. 42.0 %, $p < 0.001$). In turn, as expected, the location of the tumor itself was also significantly related to the extent of surgery (data not shown). Furthermore, patients with IDH wild-type AAs had a significantly prolonged survival when they underwent resection compared to biopsy alone (33.9 vs. 16.1 months, $p = 0.02$). One may hence hypothesize that the intrinsic biology of IDH wild-type tumors favors their development in either deeper or eloquent parts of the brain, hence restricting their ability to be resected and possibly contributing to poorer survival patterns. This is consistent with data from other retrospective studies that have demonstrated that IDH mutated gliomas are more likely to be present in the frontal lobe [29, 30], less likely to be present infratentorially [31] and more likely to be amenable to resection [32] as compared to IDH wild-type gliomas.

In conclusion, IDH mutation strongly predicts a favorable prognosis in patients with AA. Furthermore, concurrent TMZ may also be associated with improved survival in patients

with AA who are receiving adjuvant RT. As results from the CATNON Intergroup Trial (NCT00626990) [19] are still several years away, the results of this study may be considered to help guide clinical decision making in this patient population when clinical trial enrollment is not an option. Finally, the relationship between the IDH status of AAs, their location within the central nervous system and their consequent resectability may have implications for diagnosis and therapy of these tumors and should be explored further.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
CONSORT diagram

Fig. 2.

a Overall survival, stratified by TMZ receipt. **b** Overall survival, stratified by IDH status

Table 1

Baseline characteristics of patients, stratified by TMZ receipt and IDH status

	RT + TMZ (n = 136)	RT alone (n = 29)	p value	IDH mutation (n = 60)	IDH wild-type (n = 81)	p value
Age (years)	46.9 ± 14.	51.1 ± 18.1	0.17	39.1 ± 10.8	52.8 ± 15.3	<0.001
Male sex	75 (55.2 %)	16 (55.2 %)	1.00	36 (60.0 %)	45 (55.6 %)	0.60
Tumor location			0.69			<0.001
Frontal only	50/134 (37.3 %)	8/28 (28.6 %)		32/58 (55.2 %)	19 (23.5 %)	
Parietal only	17/134 (12.7 %)	6/28 (21.4 %)		8/58 (13.8 %)	12 (14.8 %)	
Occipital only	3/134 (2.2 %)	0/28 (0.0 %)		1/58 (1.7 %)	1 (1.2 %)	
Temporal only	35/134 (26.1 %)	6/28 (21.4 %)		8/58 (13.8 %)	27 (33.3 %)	
Multiple lobes or sites	22/134 (16.4 %)	6/28 (21.4 %)		9/58 (15.5 %)	13 (16.0 %)	
Other	7/134 (5.2 %)	2/28 (7.1 %)		0/58 (0.0 %)	9 (11.1 %)	
Frontal, parietal or occipital	70/134 (52.2 %)	14/28 (50.0 %)	0.83	41/58 (70.7 %)	32 (39.5 %)	<0.001
Tumor size(cm)	4.2 ± 1.9	3.5 ± 1.4	0.06	4.7 ± 1.9	3.5 ± 1.5	<0.001
Extent of resection			0.25			<0.001
Gross total resection	29 (21.3 %)	5 (17.2 %)		17 (28.3 %)	15 (18.5 %)	
Subtotal resection	50 (36.8 %)	7 (24.1 %)		32 (53.3 %)	19 (23.5 %)	
Biopsy alone	57 (41.9 %)	17 (58.6 %)		11 (18.3 %)	47 (58.0 %)	
Subtotal or gross total resection	79 (58.1 %)	12 (41.4 %)	0.10	49 (81.7 %)	34 (42.0 %)	<0.001
IDH 1/2 mutation	51/114 (44.7 %)	9/27 (33.3 %)	0.28	*	*	*
Year of diagnosis			<0.0001			0.52
2001–2003	0 (0.0 %)	19 (65.5 %)		6 (10.0 %)	13 (16.1 %)	
2004–2006	50 (36.8 %)	4 (13.8 %)		19 (31.7 %)	23 (28.4 %)	
2007–2009	57 (41.9 %)	4 (13.8 %)		25 (41.7 %)	27 (33.3 %)	
2010–2011	29 (21.3 %)	2 (6.9 %)		10 (16.7 %)	18 (22.2 %)	
Concurrent RT + TMZ	*	*	*	51 (85.0 %)	63 (77.8 %)	0.28
Adjuvant TMZ after RT	122/131 (93.1 %)	3/27 (11.1 %)	<0.0001	46/58 (79.3 %)	61/77 (79.2 %)	0.99
Treatment at recurrence			0.37			0.14
None	10/77 (13.0 %)	3/17 (17.7 %)		1/19 (5.3 %)	11/59 (18.6 %)	
Resection	14/77 (18.2 %)	7/17 (41.2 %)		6/19 (31.6 %)	11/59 (18.6 %)	
Radiation	1/77 (1.3 %)	0/17 (0.0 %)		0/19 (0.0 %)	1/59 (1.7 %)	

	RT + TMZ (n = 136)	RT alone (n = 29)	p value	IDH mutation (n = 60)	IDH wild-type (n = 81)	p value
Stereotactic radiation	1/77 (1.3 %)	0/17 (0.0 %)		1/19 (5.3 %)	0/59 (0.0 %)	
Chemotherapy	44/77 (57.1 %)	6/17 (35.3 %)		11/19 (57.9 %)	30/59 (50.9 %)	
Unknown	7/77 (9.1 %)	1/17 (5.9 %)		0/19 (0.0 %)	6/59 (10.2 %)	

* Values are not relevant

Table 2

Overall survival, stratified by either TMZ receipt or IDH status

	RT	RT + TMZ	p value	IDH wild-type	IDH mutant	p value
Median survival	31.4 months (10.6–50.0)	53.1 months (37.0–NR)	0.02	20.0 months (17.1–33.9)	111.7 months (75.7–120.2)	<0.001
One-year survival	62.1 % (42.1–76.9)	89.9 % (83.3–94.0)		73.5 % (62.3–81.8)	100 % (100.0–100.0)	
Two-year survival	55.0 % (35.3–70.9)	68.6 % (59.3–76.2)		46.1 % (34.3–57.2)	98.0 % (86.4–99.7)	
Three-year survival	44.0 % (25.6–61.0)	60.7 % (50.7–69.3)		34.9 % (23.5–46.6)	93.2 % (80.4–97.8)	
Four-year survival	33.0 % (16.7–50.2)	56.7 % (46.4–65.8)		26.9 % (16.3–38.7)	86.8 % (70.5–94.4)	
Five-year survival	29.3 % (14.0–46.5 %)	46.2 % (34.5–57.2)		22.0 % (12.1–33.9)	78.9 % (59.7–89.6)	

Table 3

Univariable and multivariable analysis for overall survival

	Univariable analysis		Multivariable analysis	
	Hazard ratio	<i>p</i> value	Hazard ratio	<i>p</i> value
Concurrent TMZ	0.56 (0.33–0.93)	0.02	0.32 (0.15–0.69)	0.004
Age at diagnosis	1.08 (1.06–1.11)	<0.001	1.05 (1.03–1.08)	<0.001
Male sex	1.11 (0.69–1.77)	0.66	1.07 (0.62–1.86)	0.81
Subtotal or gross total resection	0.30 (0.18–0.48)	<0.001	0.65 (0.37–1.14)	0.13
IDH mutation	0.11 (0.05–0.23)	<0.001	0.13 (0.05–0.35)	<0.001
Frontal, parietal or occipital	0.40 (0.24–0.65)	<0.001	0.79 (0.44–1.40)	0.41
Tumor size	0.83 (0.72–0.95)	0.009	1.00 (0.81–1.22)	0.96
Year of diagnosis	0.98 (0.89–1.09)	0.76	1.06 (0.92–1.22)	0.42