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Review Article

Role of Temozolomide Regimen on Survival Outcomes in Molecularly Stratified WHO Grade II Gliomas: A Systematic Review

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Abstract

Objective/Introduction: Although a critical chemotherapeutic, temozolomide's optimal regimen for 2016 World Health Organization (WHO) Grade II gliomas remains elusive, hence there is utility in not only cataloging survival outcomes of Grade II glioma subtypes against the background of temozolomide regimens, but also quantifying differences in progression-free survival (PFS) and overall survival (OS). **Materials and Methods:** A systematic review of MEDLINE, Embase, and Cochrane Central Register of Controlled Trails was conducted by using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and the Cochrane Handbook of Systemic Reviews of Interventions. **Results:** Each molecular subtype of WHO Grade II glioma had a different temozolomide regimen identified as optimal in prolonging PFS and OS. For PFS, with temozolomide, the 25th, 50th, and 75th percentiles, were as follows (in months), respectively–A-wt II: 6.90, 12.95, and 19.95; A-mt II: 34.45, 36.01, and 39.60; OD II: 37.90, 46.00, and 55.03 (P = 0.016). For OS, the first quartile (25%), median (50%), third quartile (75%), were respectively identified (in months–A-wt II: 21.6 (median; n = 1); A-mt II: 60.6, 85.2, and 109.8; OD II: 86.1, 96.2, and 106.3 (P = 0.37). **Conclusion:** For each tumor molecular subtype, a different temozolomide regimen was identified as optimal for prolonging PFS and OS. Furthermore, regardless of temozolomide regimen, A-wt II had a significantly shorter PFS than A-mt II and OD-II. Overall, the data can provide useful prognostic insight to patients when making critical treatment decisions. Moreover, by cataloging and assessing survival outcomes per temozolomide regimen, such may facilitate future clinical trial design.

Keywords: *Astrocytoma, glioma, low-grade glioma, oligodendroglioma, overall survival, progression-free survival, temozolomide*

Introduction

Limited knowledge of life expectancy and disease outcome can be barriers for patients to accurately understand their prognoses. Without appropriate insight, a patient may make treatment decisions that do not reflect his/her true values.[1] Such a burden may be amplified especially for low-grade gliomas (LGG), which not only are usually diagnosed during the second to fourth decades of life in typically functional patients, but also transform unpredictably to higher grades.[2,3] Unfortunately, precise data on overall survival (OS) and progression-free survival (PFS) for World Health Organization (WHO) Grade II gliomas remains elusive, as there persists to be lack of randomized controlled trials comparing treatment modalities.[4] Hence, optimal management remains contested, ranging from watch-and-wait to maximal resection, along with combinations of chemoradiotherapy.[4] Moreover, unlike WHO Grade IV gliomas, where a specific temozolomide regimen (i.e., Stupp protocol) has demonstrated survival benefit, the appropriate utilization of temozolomide in Grade II gliomas remains unknown–such is particularly important for under-resourced communities where maximal safe resection may not be available.[5,6]

Since the updated 2016 WHO classification for central nervous system tumors – which now relies upon an integrated diagnosis combining molecular markers with histology, along with evidence that Grade II gliomas stratified by molecular subtype have distinct survival outcomes and tumor microenvironments, there is possibility that optimal temozolomide regimen varies depending on Grade II glioma molecular subtype.[6-8]

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Hence, utilizing the 2016 WHO classification, this systematic review sought to provide a comprehensive catalog of all temozolomide regimens and outcomes (i.e., PFS and OS) for molecularly stratified WHO Grade II gliomas. By assessing differences in survival per specific temozolomide regimen, a better understanding can develop regarding how temozolomide regimens modulate outcome per molecular subtype. Therefore, there is potential to not only identify an optimal regimen per molecular subtype and subsequently facilitate future clinical trial design, but also provide patients with greater prognostic insight when contemplating difficult treatment decisions.

Materials and Methods

The systematic review was designed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and the Cochrane Handbook of Systematic Reviews of Interventions.[9-11]

Eligibility criteria

Study types

Only nonexperimental nonanimal clinical investigations were included.

Participants

Subjects were adult humans (18 years or older) stratified by molecular subtyped WHO Grade II gliomas.[6] Genotype definitions were as follows: Wild type astrocytomas, IDH-wild type; mutant astrocytoma, IDH-mutant with non-1p/19q codeletion; oligodendroglioma, IDH-mutant with 1p/19q codeletion. If studies characterized Grade II gliomas as positive 1p/19q codeletion (without IDH status), such tumors were imputed as oligodendrogliomas, as the vast majority of 1p/19q codeletion patients have IDH-mt.[12]

Interventions

Interventions targeting WHO Grade II gliomas were limited to those utilizing temozolomide, while excluding those exclusively involving surgery, radiotherapy, or other chemotherapies.

Outcomes

OS and progression-free survival in unit of time (days, months, years) or rate, were the values collected. OS was defined as the time of intervention to death. PFS was defined as the time of intervention to tumor recurrence/progression, characterized by radiological or clinical deterioration. Clinical deterioration involved worsening/new focal deficits or symptoms of elevated intracranial pressure. Radiologic deterioration involved increased/new tumor contrast enhancement or FLAIR hyperintensity signal changes, increased mass effect or midline shift, or volume enlargement. Definition of outcome measures from each study was also collected to confirm external consistency.

Follow up time

Follow-up time was restricted at 48 months.

Language

Only articles written in English were included.

Information sources

Medical subheadings and text words related to LGG, molecular subtypes, and treatment, were utilized for the search strategy. Medline (PubMed interface, 2008 onwards), Embase (Ovid interface, 2008 onwards), and Cochrane Central Register for Controlled Trials (Wiley interface, current issue), were all searched. 1 January 2008 was selected as the start date for the search, based the first paper subcategorizing gliomas on the IDH molecular marker.[13] In relevant literature, references were manually searched for additional trials.

Search strategy

Other than dates, no database search limitations were utilized. An electronic search examined Embase (January 1, 2008 to December 11, 2018), MEDLINE (January 1, 2008 to December 11, 2018), and Cochrane Central Register of Controlled Trails (January 1, 2008 to December 11, 2018); Appendix 1 provides the search protocols, including keywords. Specific search strategies were developed under guidance of Queen Square Institute of Neurology library and statistical services staff with expertise in systemic review searches.[14] To assess the search sensitivity and quality, robust target references were utilized–all of which were identified.[7,15-18]

Study records

Data management

Results of the literature search were imported to EndNote X9 (Clarivate Analytics, Philadelphia, Pennsylvania). Software utilization sought to reduce data entry errors and bias (i.e., deduplicating references). All investigation reports were reviewed to assess for inconsistencies (e.g., design description, outcome presentation, total patients analyzed).

Selection process

Authors screened all titles and abstracts independently on the basis of the inclusion criteria. Literature meeting inclusion criteria was reviewed in full, to assess appropriateness for ultimate entry into in the systematic review.

Data items

In accordance with recommendations from the Cochrane Handbook for Systematic Reviews of Interventions (chapter 7), the following data was collected into a Microsoft Excel spreadsheet: Author, publication year, journal citation; setting; inclusion and exclusion

criteria; study design; study population; tumor details at diagnosis (tumor size, location, and histology); risk of bias (including assessment of bias); length of follow-up; outcomes (OS, PFS).[19]

Data synthesis

Data was placed into tables permitting for comparison of OS and PFS, stratified by tumor type and temozolomide regimen. A quantile-quantile plots were produced for the PFS and OS data, which demonstrated both datasets as nonnormally distributed (even with transformations). Secondary to the nonnormal distribution, when the data was pooled (cases with $n = 1$ were excluded), the summary measures included the 25-percentile, median, and 75-percentile; 95-percentile confidence interval of the median could not be determined due to the small number of identified studies. Meanwhile, a nonparametric Kruskal–Wallis test was performed to determine if the survival outcomes stratified by genotype were significantly different; next an analysis was conducted utilizing the independent Wilcoxon rank sum test.[20,21] All analysis was run through R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria).[22]

Results

The search of Medline, Embase, and Central yielded a total of 8311 abstracts [Figure 1]. Four more manuscripts were added upon sifting through systematic reviews identified in our search. After duplicates were removed, we screened 7542 texts by reading the title and full abstracts. From these, 7475 were excluded for not conforming to inclusion criteria, while 67 were flagged for further review in the full-text assessment phase. Of the 67, 61 articles were removed for not examining temozolomide, for not providing raw PFS/OS data in the form of day/month/year (many abstracts met inclusion criteria, however provided data in the form of hazards ratios, *P* values, or Kaplan–Meier graphs without the ability to extract raw PFS or OS), or being systematic reviews. Ultimately, six manuscripts were included for quantitative synthesis in the form of Tables 1 and 2.

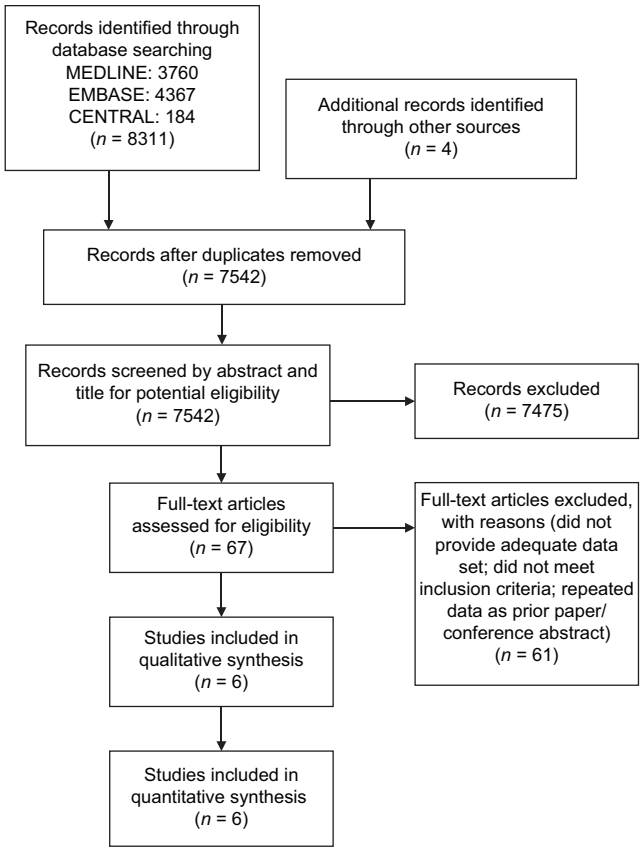

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis

Progression-free survival data

From the six studies, five provided PFS data [Table 1]. Four studies were prospective (with one randomized) and one retrospective.[7,17,23-25] Two examined a dose-dense regimen, one a low-dose, and two others varied by the number of cycles (i.e., greater than or less than 12-cycles).[7,17,23-25]

Examining high risk tumors, Baumert *et al*. conducted a randomized open label phase 3 intergroup study of a dose-dense temozolomide regimen, consisting of 75 mg/m^2 daily for 21 days, repeated every 28 days for 12 cycles maximum [Table 1]; median PFS for OD-II, A-mt II, and A-wt II were as follows: 55.03, 36.01, and 23.69 months.[7] The other dose-dense regimen was from another prospective single arm phase II study by Pellerino *et al*., which investigated temozolomide 1 week on/1 week off, for a median of 11 cycles (range, 2–18 cycles); OD-II had a PFS of 46 months.[24]

Meanwhile, Houillier *et al*. retrospectively investigated the role of temozolomide administered daily for 5-days at 200 mg/m^2, repeated every 28 days for at least 12 cycles (or up to 30 cycles).[23] PFS for OD-II, A-mt II, and A-wt II were respectively: 37.9, 32.9, and 18.7 months.[23] Similarly, examining temozolomide administered daily for 5-days at 200 mg/day repeated every 28 days, but rather for 12 cycles maximum, the prospective trial by Wahl *et al*. found PFS for OD-II, A-mt II, and A-wt II to be respectively: 58.8, 43.2, and 7.2 months.[17]

Lastly, one study (prospective phase II open label) examined low-dose temozolomide 50 mg/mq/day, 1 week on/1 week off, until progression or for a maximum of 24 months, found PFS for OD-II and A-wt II to be 35 and 6 months, respectively.[25]

After pooling data based on genotype, a Kruskal-Wallis test found significant differences in median PFS ($P = 0.016$) after temozolomide treatment, subsequently Wilcoxon ranked sum tests identifying A-wt II PFS as significantly different to A-mt II and OD-II [Table 2]. The 25th percentile, median (50th percentile), and 75th percentile for PFS was then found, respectively–A-wt II: 6.90, 12.95,

Table 1: Progression free survival and overall survival stratified by tumor molecular subtype and temozolomide treatment

Study	Median follow-up (months)	*n*	Molecular Subtype	Treatment	Median PFS (months)		Median PFS (3-Years %)	Median PFS (5-Years %)
Baumert *et al.*, 2016[7]	48 months	89	Astrocytoma-mutant II, high risk	Radiotherapy	55.36 (95% CI: 47.87-65.87)	HR 1.86 (95% CI, 1.21-2.87), log-rank P=0.0043		42.50% (95% CI: 27.38-56.83)
		76	Astrocytoma-mutant II, high risk	Temozolomide (dose dense, 75 mg/m^2 daily, for 21 days, repeated every 28 days, for 12 cycles maximum)	36.01 (95% CI: 28.42-46.95)			19.43% (95% CI: 8.87-33.00)
		45	Oligodendroglioma II, high risk	Radiotherapy	61.63 (95% CI: 42.32-NR)	No Significant treatment-dependent differences		58.49% (95% CI: 39.43-73.41)
		59	Oligodendroglioma II, high risk	Temozolomide (dose dense, 75 mg/m^2 daily, for 21 days, repeated every 28 days, for 12 cycles maximum)	55.03 (95% CI: 37.95-NR)			47.39% (95% CI: 30.71-62.35)
		29	Astrocytoma-wild type II, high risk	Radiotherapy	19.09 (95% CI: 11.27-25.69)	No Significant treatment-dependent differences		0% (95% CI: 0.00-0.00)
		20	Astrocytoma-wild type II, high risk	Temozolomide (dose dense, 75 mg/m^2 daily, for 21 days, repeated every 28 days, for 12 cycles maximum)	23.69 (95% CI: 5.55-42.25)			17.78% (95% CI: 3.69-40.48)
Houillier *et al.*, 2010[23]	63.4 months	74	Oligodendroglioma II	Temozolomide (daily for 5 days, at 200 mg/m^2, repeated every 28 days, at least 12 cycles or up to 30)	37.9	These differences did not reach significance		
			Astrocytoma-mutant II	Temozolomide (daily for 5 days, at 200 mg/m^2, repeated every 28 days, at least 12 cycles or up to 30)	32.9			
			Astrocytoma-wild Type II	Temozolomide (daily for 5 days, at 200 mg/m^2, repeated every 28 days, at least 12 cycles or up to 30)	18.7			
Pellerino *et al.*, 2017[24]	64 months	21	Oligodendroglioma II	Temozolomide (dose dense, 1 week on/1 week off, median 11 cycles, range 2-18 cycles)	46		71.40	28.60%
		24	IDH-wild type	Temozolomide (dose dense, 1 week on/1 week off, median 11 cycles, range 2-18 cycles)	34		45.80	25.00%
Wahl *et al.*, 2017[17]	90 months	44	Oligodendroglioma II (imputed)	Temozolomide (daily for 5 days, at 200 mg/day, repeated every 28 days, up to 12 cycles)	58.8 (95% CI: 45.6-NA)	P=0.01		
		31	Astrocytoma-mutant II	Temozolomide (daily for 5 days, at 200 mg/day, repeated every 28 days, up to 12 cycles)	43.2 (95% CI: 25-64.8)			
		13	Astrocytoma-wild type II	Temozolomide (daily for 5 days, at 200 mg/day, repeated every 28 days, up to 12 cycles)	7.2 (95% CI: 4.8-NA)			
Villani *et al.*, 2017[25]	54 months	10	Oligodendroglioma II (imputed)	Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 week off, until progression or for maximum of 24 months)	35	P<0.04		
		2	No 1p19q Codeletion	Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 week off, until progression or for maximum of 24 months)	5			
		7	IDH-mutant	Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 week off, until progression or for maximum of 24 months)	36	P<0.009		
		4	Astrocytoma-wild type II	Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 week off, until progression or for maximum of 24 months)	6			

Contd...

Table 1: Contd...

Study	Median follow-up (months)	*n*	Molecular subtype	Treatment	Median OS (months)	*P*	Median OS (3-Years %)	Median OS (5-Years %)
Gao *et al*., 2018[26]	48 months	41	Astrocytoma-mutant II, High Risk	Temozolomide (dose dense, 75 mg/m^2 daily, for 21 days, repeated every 28 days, for 12 cycles maximum)	36	<0.01		
		51	Astrocytoma-mutant II, High Risk	Radiotherapy	55.4			
Pellerino *et al*., 2017[24]	64 months	15	Oligodendroglioma II	Temozolomide (dose dense, 1 week on/1 week off, median 11 cycles, range 2-18 cycles)	76		90.50%	66.70%
Wahl *et al*., 2017[17]	90 months	44	Oligodendroglioma II	Temozolomide (daily for 5 days, at 200 mg/day, repeated every 28 days, up to 12 cycles)	116.4 (95% CI: 87.6-NA)	<0.001		
		31	Astrocytoma-mutant II	Temozolomide (daily for 5 days, at 200 mg/day, repeated every 28 days, up to 12 cycles)	134.4 (95% CI: 82.8-NA)			
		13	Astrocytoma-wild type II	Temozolomide (daily for 5 days, at 200 mg/day, repeated every 28 days, up to 12 cycles)	21.6 (95% CI: 13.2-NA)			

CI – Confidence interval; NA – Not available; OS – Overall survival; PFS – Progression free survival, IDH – Isocitrate dehydrogenase mutation

and 19.95 months; A-mt II: 34.45, 36.01, and 39.60 months; OD-II: 37.90, 46.00, and 55.03 months [Table 2]. Figure 2 exhibits a graphical representation stratified by temozolomide regimen and tumor genotype.

Overall survival data

Only three studies provided OS data [Table 1], yet all were prospective.[17,24,26]

Two of the studies examined dose-dense regimens.[24,26] For OD-II treated by dose-dense temozolomide 1 week on/1 week off for a median of 11 cycles (range 2–18 cycles), Pellerino *et al*. identified an OS of 76 months.[24] Meanwhile, in the other dose-dense regimen, Gao *et al*. found a median OS of 36 months, for high risk A-wt II treated postoperatively with oral temozolomide 75 mg/m^2 daily for 21 days, repeated every 28 days for 12 cycles maximum.[26]

Finally, for patients with gross residual disease postsurgical resection, Wahl *et al*. found those who received temozolomide daily for 5-days at 200 mg/day repeated every 28 days (up to 12 cycles), the OS for OD-II, A-mt II, and A-wt II, was respectively 116.4, 134.4, and 21.6 months.[17]

The data for temozolomide treated tumors stratified by genotype was pooled and analyzed by a Kruskal-Wallis test, which did not find the three tumor types to have significantly different median OS (P = 0.37). Wilcoxon ranked sum tests further confirmed variation in OS by genotype to not be significantly different [Table 2]. Nevertheless, the 25th percentile, median (50th percentile), and 75th percentile for OS stratified by genotype were found, respectively–A-wt II (n = 1): 21.6, 21.6, and 21.6 months; A-mt II: 60.6, 85.2, and 109.8 months; OD-II: 86.1, 96.2, and 106.3 months [Table 2]. Figure 2 provides a graphical representation of OS stratified by temozolomide regimen and tumor genotype.

Discussion

General considerations

Despite limitations in available number of studies, this systematic review provides a comprehensive catalog of all temozolomide investigations examining WHO grade II gliomas stratified by genotype. Furthermore, there are several core findings which can be extracted to provide direction for future clinical trial design. First, regardless of temozolomide regimen, A-wt II tumors had the shortest PFS at 12.95 months (25th and 75th percentiles: 6.90, 19.95 months), significantly shorter than both A-mt II (median: 36.01 months) and OD-II (46.00 months) [Table 2], confirming trends in prior studies that regardless of treatment type genotype dictates prognosis.[14,27-30]

Second, for OS, our data demonstrated no statistically significant differences between OD-II, A-mt II, or

Table 2: Interquartile range, median, and confidence interval for progression-free survival and overall survival stratified by tumor molecular subtype

PFS	PFS 25th quartile (months)	PFS Median (months)	PFS 75th quartile (months)	Kruskal-Wallis Test (Kruskal-Wallis χ^2)	Wilcoxon Ranked Sum Test Estimated Difference	
					Astrocytoma-mutant II	Oligodendroglioma II
Astrocytoma-wild Type II	6.90	12.95	19.95	8.2154 *P*=0.016	25.1 (95% CI: 9.21-37.20) W=0, *P*=0.057	31.62 (95% CI: 14.21-51.60) W=0, P=0.016
Astrocytoma-mutant II	34.45	36.01	39.60			9.99 (95% CI: −8.2-25.9)
Oligodendroglioma II	37.90	46.00	55.03			W=3, *P*=0.25
OS	**OS 25th quartile (months)**	**OS Median (months)**	**OS 75th quartile (months)**	**Kruskal-Wallis Test (Kruskal-Wallis χ^2)**	**Wilcoxon ranked sum test Estimated difference**	
					Astrocytoma-mutant II	**Oligodendroglioma II**
Astrocytoma-wild type II	21.6	21.6	21.6	2 *P*=0.3679	63.6 (95% CI: 14.4-112.8) W=0, *P*=0.67	74.6 (95% CI: 54.4-94.8) W=0, *P*=0.67
Astrocytoma-mutant II	60.6	85.2	109.8			11 (95% CI: -54.4-80.4)
Oligodendroglioma II	86.1	96.2	106.3			W=2, *P*=1

CI – Confidence interval; OS – Overall survival; PFS – Progression free survival

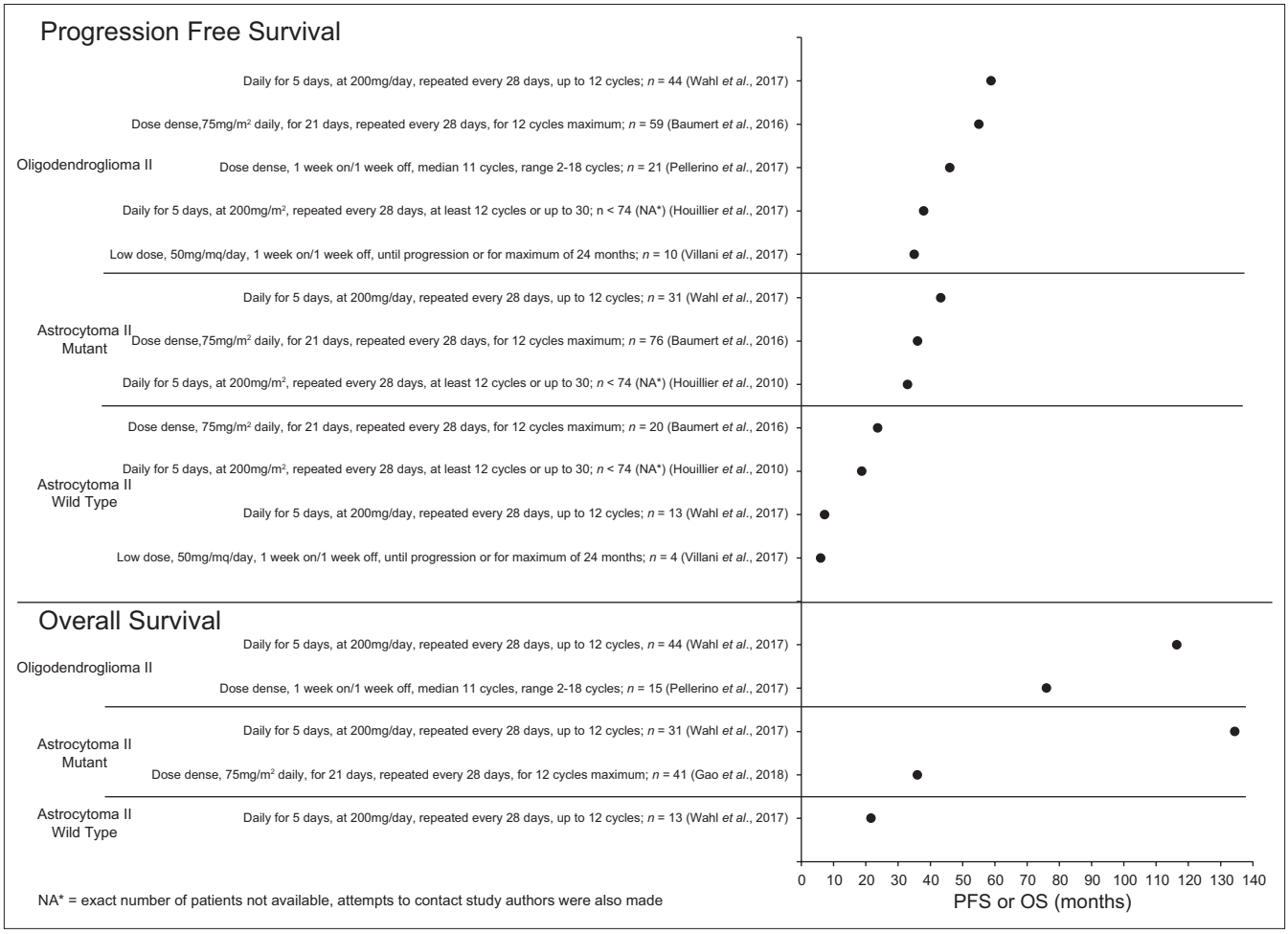

Figure 2: Progression-free survival and overall survival stratified by 2016 World Health Organization Grade II glioma subtype and temozolomide treatment

A-wt II tumors [Table 2]. However, likewise to PFS, A-wt II tumors (median: 21.6 months) had a shortest OS, followed by A-mt II (85.2 months) and OD II (96.2). The observation may be explained by mass spectroscopy data that tumor subtypes have distinct immunosuppressive microenvironments.[8] The variation in microenvironment may potentially enhance responsiveness of OD II to temozolomide much more, than to A-wt II and A-mt II tumors.[8] Moreover, this observation could have arisen secondary to OD-II tumors having earlier treatment with temozolomide than A-mt II, and with A-mt II tumors more likely to undergo postoperative watch-and-wait.[31,32]

Regardless, the finding highlights the utility in stratifying treatments and exclusively examining temozolomide regimens.

Progression-free survival-World Health Organization, grade II astrocytoma, *wild type*

When examining the raw data for PFS, several trends are recognized [Figure 2]. For A-wt II patients, the temozolomide treatment that yielded the longest PFS (23.69 months) was with a postoperative dose dense regimen, 75 mg/m^2 daily for 21 days, repeated every 28 days for 12 cycles maximum.[7] This same dose dense regimen also yielded the longest PFS for A-wt II when accounting for all other nontemozolomide forms of treatment.[7,14] The second longest PFS (18.7 months) was another dose-dense temozolomide regimen administered daily for 5-days at 200 mg/m^2, repeated every 28 days for at least 12 cycles (or up to 30 cycles).[23] When this same regimen was administered for up to 12 cycles, PFS dropped to 7.2 months, thus implying more cycles of temozolomide may improve survival.[17,23] Finally, the low dose temozolomide regimen of 50 mg/mq/day, 1 week on/1 week off, until progression or for a maximum of 24 months, resulted in the shortest PFS of 6 months.[25] Hence, to lengthen PFS for A-wt II tumors, dose dense temozolomide at 75 mg/m^2 daily for 21 days, repeated every 28 days for 12 cycles maximum appears the optimal choice, especially when considering the toxicity profile of dose dense and standard schedule are comparable, yet the small number of studies precludes safe conclusions from being made.[33]

Overall survival-World Health Organization, grade II astrocytoma, wild type

Regarding OS, only one temozolomide study was cataloged for A-wt II. The regimen of temozolomide daily for 5-days at 200 mg/m^2, repeated every 28 days up to 12 cycles, yielded an OS of 21.6 months.[17] Hence, for elucidating the best chemotherapy regimen for A-wt II tumor OS stratified by temozolomide, more studies are needed [Figure 2].

Progression-free survival-World Health Organization, grade II astrocytoma, mutant

For A-mt II tumors, the treatment regimen with temozolomide daily for 5-days at 200 mg/m^2, repeated every 28 days up to 12 cycles provided the longest PFS, at 43.2 months [Figure 2].[17] Meanwhile, when the number of cycles was extended past 12, PFS dropped to 32.9 months.[23] Hence, for A-mt II tumors, less cycles of the same temozolomide regimen prolonged PFS, contrary to A-wt II tumors where PFS decreased with less cycles of the same regimen. Such a distinction between tumor genotype and number of cycles potentially results from different immunosuppressive microenvironments between A-wt and A-mt tumors, which in turn modulates the tumor susceptibility to temozolomide dosage.[8] Meanwhile, when given a dose-dense regimen of temozolomide 75 mg/m^2 daily for 21 days, repeated every 28 days for 12 cycles maximum, PFS was an intermediate value of 36.01 months.[7]

Overall survival-World Health Organization, grade II astrocytoma, mutant

Two studies were available for examining OS of A-mt II tumors.[17,26] Paralleling PFS, the regimen of temozolomide daily for 5-days at 200 mg/m^2, repeated every 28 days up to 12 cycles, yielded the longer OS, at 134.4 months; hence, this regimen may be most optimal for A-mt II with regards to OS and PFS.[17] Meanwhile, the dose dense regimen of 75 mg/m^2 daily for 21 days, repeated every 28 days for 12 cycles maximum, yielded a lower OS of 36 months.[26] Despite the large difference between regimens, a robust investigation with a homogenous study population is needed prior to making conclusions supporting one regimen over another.

Progression-free survival-World Health Organization, grade II oligodendroglioma

For OD-II, five studies investigated temozolomide dosages.[7,17,23-25] Of these, the regimen of temozolomide daily for 5-days at 200 mg/m^2, repeated every 28 days up to 12 cycles produced the longest PFS (58.8 months); notably longer than the same regimen extended for at least 12 cycles (37.9 months).[17,23] The two dose-dense regimens yielded the second and third respective longest PFS, at 55.03 and 46 months.[7,24] Finally, the low-dose regimen of 50 mg/mq/day, 1 week on/1 week off, until progression or for a maximum of 24 months, resulted in the shortest PFS at 35 months [Figure 2].[25] However, relative to temozolomide treatments, those that utilize a combination of RT with CT are recognized to produce the longest PFS (120.2 and 162 months) for OD-II, yet notwithstanding our results indicate OD-II is potentially sensitive to different temozolomide dosages.[7,14,17,23-25]

Overall survival-World Health Organization, grade II oligodendroglioma

Amongst OD-II tumors, OS values stratified by temozolomide dosage was only comparable between two regimens [Figure 2]. Those receiving temozolomide daily for 5-days at 200 mg/m^2, repeated every 28 days up to 12 cycles, experienced the longer OS of 116.4 months, relative to the dose-dense regimen of 1 week on/1 week off for a median of 11 cycles yielded 76 months.[17,24] Likewise, with PFS, for OD-II the nontemozolomide treatment regimens yield the longest OS values (i.e., 235.4 months with RT; 212.4 months with RT and CT).[34]

Study limitations

To place the data collected from this systematic review into context, a number of limitations should be recognized. First, several studies implied definitions for PFS and OS, rather than explicitly defining the parameters. Moreover, in

the studies where tumors were resected, there was no data providing raw PFS and OS values stratified by extent of tumor resection and temozolomide regimen; the potential for heterogeneity in extent of resection across studies is important to note, as extent of resection has been shown to independently influence survival.[16,18] Furthermore, in the method sections of some studies, inclusion and exclusion criteria were minimally described. Likewise, demographic data was not uniformly presented or available stratified by molecular marker and temozolomide regimen, thus limiting application of results to the broader population.

In addition, although only one study was retrospective, the inconsistent follow-up times amongst the investigations reduces the strength in comparing results side by side. Finally, most of the studies involved small samples sizes, further limiting the conclusions of any one investigation. Notwithstanding these limitations, by conducting this review and presenting survival outcomes, highlights not only the large variability in temozolomide regimens utilized globally and how an optimal regimen has yet to be agreed upon, but also the restrictions current studies impose when externally comparing results. Hence, recognizing these problems will allow future clinical trial design to potentially improve. Yet, by extension currently no treatment recommendations can be made from this review. In the future, investigations stratifying by molecular subtypes should also aim at collecting data on temozolomide resistance and adverse effects, as well as proportion of tumors which progress to higher grades – for such information could provide valuable insight in selecting treatments.

Conclusion

This systematic review provided a comprehensive catalog of all temozolomide regimens stratified by WHO Grade II glioma molecular subtype. Several observations were made regarding survival outcomes. Median OS for A-wt II (21.6 months), A-mt II (85.2 months), and OD-II (96.2 months) were found, as were median PFS for A-wt II (12.95 months), A-mt (36.01 months), and OD-II (46.00 months). Overall, A-wt II was confirmed to have a significantly shorter PFS than A-mt II and OD II; however, there was no significant difference found between PFS of OD II with A-mt II. Additionally, for temozolomide treatment, all three molecular subtypes were not found to have statistically significant differences in OS, despite differences in PFS. Moreover, there was a general observation that a different optimal temozolomide regimen exists depending on the WHO grade II glioma's genotype. Hence, despite the limitations precluding robust conclusions, by cataloguing the survival outcomes of temozolomide regimens amongst the background of tumor genotype, this review provides an avenue for improving future clinical trial design, as well as better informing patients about their prognosis.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflicts of interest

There are no conflicts of interest.

References

1. Weeks JC, Cook EF, O'Day SJ, Peterson LM, Wenger N, Reding D, *et al*. Relationship between cancer patients' predictions of prognosis and their treatment preferences. JAMA 1998;279:1709-14.
2. Grier J. Low-grade gliomas in adults. Oncologist 2006;11:681-93.
3. Whittle IR. The dilemma of low grade glioma. J Neurol Neurosurg Psychiatry 2004;75:ii31-6.
4. Pouratian N, Schiff D. Management of low-grade glioma. Curr Neurol Neurosci Rep 2010;10:224-31.
5. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. New England. J Med 2005;352:987-96.
6. Louis D, Ohgaki H, Wiestler O, Cavenee W. WHO Classification of Tumours of the Central Nervous System. 4th ed. Lyon, France: WHO/IARC; 2016.
7. Baumert BG, Hegi ME, van den Bent MJ, von Deimling A, Gorlia T, Hoang-Xuan K, *et al*. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): A randomised, open-label, phase 3 intergroup study. Lancet Oncol 2016;17:1521-32.
8. Fu W, Wang W, Li H, Jiao Y, Weng J, Huo R, *et al*. High dimensional mass cytometry analysis reveals characteristics of the immunosuppressive microenvironment in diffuse astrocytomas. Front Oncol 2020;10:78.
9. Higgins J, Altman D, Gotzsche P, Juni P, Moher D, Oxman A, *et al*. The Cochrane Collaboration's Tool for Assessing Risk of Bias in randomised trials. BMJ 2011;343:d5928-928.
10. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 2015;349:7647.
12. Reuss DE, Sahm F, Schrimpf D, Wiestler B, Capper D, Koelsche C, *et al*. ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma. Acta Neuropathol 2015;129:133-46.
13. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, *et al*. An integrated genomic analysis of human glioblastoma multiforme. Science 2008;321:1807-12.
14. Ghaffari-Rafi A, Samandouras G. Effect of treatment modalities on progression-free survival and overall survival in molecularly subtyped world health organization grade II diffuse gliomas: A systematic review. World Neurosurg 2020;133:366-8000.
15. Buckner J, Giannini C, Eckel-Passow J, Lachance D, Parney I,

Laack N, *et al*. Management of diffuse low-grade gliomas in adults-use of molecular diagnostics. Nat Rev Neurol 2017;13:340-51.
16. Jakola AS, Skjulsvik AJ, Myrmel KS, Sjåvik K, Unsgård G, Torp SH, *et al*. Surgical resection versus watchful waiting in low-grade gliomas. Ann Oncol 2017;28:1942-8.
17. Wahl M, Phillips JJ, Molinaro AM, Lin Y, Perry A, Haas-Kogan DA, *et al*. Chemotherapy for adult low-grade gliomas: Clinical outcomes by molecular subtype in a phase II study of adjuvant temozolomide. Neuro Oncol 2017;19:242-51.
18. Wijnenga MM, French PJ, Dubbink HJ, Dinjens WN, Atmodimedjo PN, Kros JM, *et al*. The impact of surgery in molecularly defined low-grade glioma: An integrated clinical, radiological, and molecular analysis. Neuro Oncol 2018;20:103-12.
19. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Ver. 5.1.0. Cochrane Collaboration; 2011. Available from: http://www.cochrane-handbook.org. [Last accessed on 2020 Oct 12].
20. Kruskal WH, Allen Wallis H. Use of ranks in one-criterion variance analysis. J Am Statistical Assoc 1952;47:260, 583-621.
21. Wilcoxon F. Individual comparisons by ranking methods. Biometrics Bulletin 1945;1:80-3.
22. Core Team R. A language and Environment for Statistical Computing. Foundation for Statistical Computing, Vienna, Austria; 2018. Available from: http://www.R-project.org/. [Last accessed on 2020 Oct 12].
23. Houillier C, Wang X, Kaloshi G, Mokhtari K, Guillevin R, Laffaire J, *et al*. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology 2010;75:1560-6.
24. Pellerino A, Franchino F, Pace A, Carapella C, Dealis C, Caroli M, *et al*. Temozolomide (TMZ) 1 week on/1 week off as initial treatment for high risk low grade oligodendroglial tumors: A phase II aino (Italian Association for Neuro-Oncology) study. Neuro-Oncol 2017;19 Suppl 3:iii21.
25. Villani V, Merola R, Vidiri A, Fabi A, Carosi M, Giannarelli D, *et al*. Temozolomide low-dose chemotherapy in newly diagnosed low-grade gliomas: Activity, safety, and long-term follow-up. Tumori 2017;103:255-60.
26. Gao Y, Weenink B, van den Bent MJ, Erdem-Eraslan L, Kros JM, Sillevis Smitt P, *et al*. Expression-based intrinsic glioma subtypes are prognostic in low-grade gliomas of the EORTC22033-26033 clinical trial. Eur J Cancer 2018;94:168-78.
27. Etxaniz O, Carrato C, de Aguirre I, Queralt C, Muñoz A, Ramirez JL, *et al*. IDH mutation status trumps the Pignatti risk score as a prognostic marker in low-grade gliomas. J Neurooncol 2017;135:273-84.
28. Minichillo S, Franceschi E, Mura A, Tosoni A, Tallini G, Pession A, *et al*. The role of treatments in IDH mutant molecular astrocytomas. Ann Oncol 2017;28 Suppl 6:vi76.
29. Li MY, Wang YY, Cai JQ, Zhang CB, Wang KY, Cheng W, *et al*. Isocitrate dehydrogenase 1 Gene Mutation Is Associated with Prognosis in Clinical Low-Grade Gliomas. PLoS One 2015;10:e0130872.
30. Metellus P, Coulibaly B, Colin C, De Paula AM, Vasiljevic A, Taieb D, *et al*. Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis. Acta Neuropathol 2010;120:719-29.
31. Straube C, Kessel KA, Schmidt-Graf F, Krieg SM, Meyer B, Gempt J, *et al*. A trend towards a more intense adjuvant treatment of low-grade-gliomas in tertiary centers in Germany after RTOG 9802 Results from a multi-center survey. BMC Cancer 2018;18:907.
32. van den Bent MJ. Oligodendrogliomas: A short history of clinical developments. CNS Oncol 2015;4:281-5.
33. Pouratian N, Gasco J, Sherman JH, Shaffrey ME, Schiff D. Toxicity and efficacy of protracted low dose temozolomide for the treatment of low grade gliomas. J Neurooncol 2007;82:281-8.
34. Youland RS, Kreofsky CR, Schomas DA, Brown PD, Buckner JC, Laack NN. The impact of adjuvant therapy for patients with high-risk diffuse WHO grade II glioma. J Neurooncol 2017;135:535-43.

Appendix Legend

Appendix 1: Search terms

Pubmed (MEDLINE)

(A)
- (1) molecula*
- (2) genetic* or genetics or genetic
- (3) mutation* or mutation
- (4) molecular genetic* or molecular genetic or molecular genetics

(B)
- (1) overall survival* or overall survival or overall survivals
- (2) survival* or survival or survivals
- (3) "os"

(C)
- **(1)** progression free survival* or progression free survival or progression free survivals
- **(2)** progression* or progression or progressions or PFS or PFSs

(1) low grade glioma or LGG or LGGs
(2) grade 2 gliomas or grade ii gliomas
(3) astrocytoma* or astrocytomas
(4) oligodendroglioma* or oligodendrogliomas

(D)
- **(1)** Treatment* or treatments or treatment
- **(2)** Treat* or treat or treats

Publication date from 2008/01/01 to 2018/12/31

Search **((((((((((((overall survival*) OR overall survival) OR overall survivals) OR survival*) OR survival) OR survivals) OR "os"))) OR (((((((((progression free survival*) OR progression free survival) OR progression free survivals) OR progression*) OR progression) OR progressions) OR PFS) OR PFSs)))) AND ((((molecula*) OR (((genetic*) OR genetics) OR genetic)) OR ((mutation*) OR mutation)) OR (((molecular genetics) OR molecular genetic) OR molecular genetic*))) AND (((((((low grade glioma) OR LGG) OR LGGs)) OR ((grade 2 gliomas) OR grade ii gliomas)) OR ((astrocytoma*) OR astrocytomas)) OR ((oligodendroglioma*) OR oligodendrogliomas))) AND ((((((treatment*) OR treatments) OR treatment) OR treat*) OR treat) OR treats)**

Embase Ovid

1. exp glioma/
2. glioma*.mp.
3. LGG*.mp.
4. astrocytoma*.mp.
5. oligodendroglioma*.mp.
6. (grade adj ii).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp progression free survival/
9. (progression adj free).mp.
10. progression*.mp.
11. PFS*.mp.
12. 8 or 9 or 10 or 11
13. exp overall survival
14. (overall adj survival*).mp.
15. OS*.mp.
16. 13 or 14 or 15
17. exp molecular genetics
18. (molecular adj genetic*).mp.
19. molecul*.mp.
20. genetic*.mp.
21. 17 or 18 or 19 or 20
22. treatment*.mp.
23. 12 or 16
24. 7 and 21 and 22 and 23
25. 24 and 2008:2018.(sa_year).

Key:

mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term wor

CENTRAL

1. MeSH descriptor: [Glioma] explode all trees
2. glioma*
3. astrocytoma*
4. oligodendroglioma*
5. LGG*
6. #2 or #3 or #4 or #5
7. # 1 or #6
8. MeSH descriptor: [Disease-Free Survival] explode all trees
9. progression*
10. survival*
11. PFS*
12. #9 or #10 or #11
13. #8 or #12
14. OS*
15. overall*
16. #14 or #15
17. #13 or #16
18. MeSH descriptor: [Molecular Biology] explode all trees
19. genetic*
20. molecul*
21. #18 or #19 or #20
22. MeSH descriptor: [Therapeutics] explode all trees
23. treatment*
24. #22 or #23
25. #7 and #17 and #21 and #24