NEUROLOGY INDIA
Publication of the Neurological Society of India

REVIEW ARTICLE

Year : 2022 | **Volume** : 70 | **Issue** : 3 | **Page** : 864--871

Is There a Role for Temozolomide in Glioma Related Seizures? A Systematic Review

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Abstract

Background: Seizures often herald the clinical appearance of glioma. Temozolomide (TMZ) is the first-line chemotherapeutic agent that has been used to treat glioma. **Objective:** We conducted a systematic review to determine seizure outcomes in glioma patients treated with TMZ. **Methods and Material:** We searched EMBASE and PubMed databases (January 1, 2003–August 26, 2021) by using search terms closely related to glioma, seizure, and temozolomide. Titles, abstracts, and full texts were screened and selected using previously established inclusion and exclusion criteria. The research team members reviewed potential articles and reached a consensus on the final articles to be included. **Results:** Nine studies containing data from three continents met our inclusion criteria. From several descriptive studies on low-grade gliomas (LGGs), the percentage of patients with partial seizure control after TMZ treatment ranged from 29% to 89.7%, and the percentage of patients with complete seizure control after TMZ ranged from 19.4% to 72%. In a retrospective cohort study of patients with LGGs, there was a marked difference in decreased seizure frequency between patients receiving TMZ and those who did not receive TMZ. In a randomized trial, TMZ seemed to have little effect on seizure control in elderly patients with glioblastoma. **Conclusions:** At present, there are few high-quality and well-designed clinical studies on TMZ for gliomas-related seizures. In terms of the literature included in this review, TMZ has an inhibitory effect on epilepsy. More randomized controlled trials are needed to elucidate the clinical benefits of TMZ in the treatment of gliomas-related seizures.

How to cite this article:
Yue J, Yin C, Chen L, Xu R, Zhao D. Is There a Role for Temozolomide in Glioma Related Seizures? A Systematic Review.Neurol India 2022;70:864-871

How to cite this URL:
Yue J, Yin C, Chen L, Xu R, Zhao D. Is There a Role for Temozolomide in Glioma Related Seizures? A Systematic Review. Neurol India [serial online] 2022 [cited 2022 Aug 4];70:864-871
Available from: https://www.neurologyindia.com/text.asp?2022/70/3/864/349588

Full Text

Gliomas represent four-fifths of malignant brain tumors[1],[2] Seizures are a typical manifestation of gliomas, particularly supratentorial low-grade gliomas (LGGs), and substantially impair quality of life.[3],[4],[5],[6] In addition, seizures, either at presentation or during the follow-up, are common in high-grade gliomas (HGGs; e.g., glioblastoma multiforme, GBM) with a frequency that ranges from 30% to 50%)[7],[8],[9] Epileptic

seizure incidence varies with brain tumor location, grade, and subtype; one can observe a reduction in epileptogenicity from LGGs to HGGs.[6],[10] It is recommended to begin antiepileptic therapy after the first seizure in patients with gliomas as there is a greater risk of recurrence.[11],[12]

Temozolomide (TMZ), an oral DNA-alkylating chemotherapeutic drug that delivers a methyl group to purine bases of DNA (O6-guanine, N7-guanine, and N3-adenine), is frequently applied together with radiotherapy (RT) as part of the frontline management of malignant gliomas.[13],[14],[15] TMZ has been shown to be active and well tolerated in patients suffering from various subtypes of progressive LGGs.[15],[16] Studies have demonstrated that postsurgical adjuvant TMZ chemotherapy can prolong the survival time of patients with malignant gliomas from 12.1 months to 14.6 months.[17] Interestingly, TMZ chemotherapy has also been speculated to provide clinical benefits in glioma patients with epileptic seizures. Amelioration in seizure frequency was seen in 15 of 28 patients with World Health Organization (WHO) grade II cerebral gliomas, with six patients becoming seizure-free post TMZ treatment.[18] Similarly, in a study of 31 subjects who were treated with TMZ, six patients achieved complete seizure control and nine patients obtained partial seizure control.[19] TMZ is distinguished from classical or newer antiepileptic drugs, such as valproic acid, levetiracetam, and lacosamide; however, the antiepileptic benefit of TMZ in different grades of gliomas has been reported several times in the past decade.[18],[19],[20],[21],[22],[23] While there are some single-institution prospective or retrospective case series that have investigated the relationship between gliomas-associated seizures and TMZ treatment, there is currently no comprehensive systematic literature review that can identify the antiepileptic effect of TMZ. Therefore, the aim of this study is to determine the antiepileptic effect of TMZ chemotherapy on patients with different grades gliomas who suffered from epileptic seizures.

Methods

As a template for the methodology, this study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] This work was not registered as a systematic review protocol in the Cochrane database.

Search strategy

The search strategy involved querying the electronic databases PubMed and EMBASE from January 1, 2003 to August 26, 2021. The keywords and Medical Subject Headings (MeSH) used for searching were the following: (”temozolomide” OR “TMZ”) AND (”seizure” OR “epilepsy” OR “seizures” OR “convulsion” OR “epileptic”) AND (”glioma” OR “glioblastoma” OR “oligodendroglioma” OR “astrocytoma” OR “oligo-astrocytoma” OR “anaplastic gliomas”). Papers were selected independently by two authors according to the titles and abstracts. All publications with abstracts and full texts were restricted to those involving human subjects and those written in the English language.

Study inclusion

Studies were selected if all of the following inclusion criteria were met: (1) original research studies regarding patients with clinically confirmed gliomas; (2) those involving temozolomide chemotherapy; (3) studies including data on at least five patients; (4) articles containing sufficient information on the outcomes of gliomas-associated seizures after temozolomide treatment; (5) case series, cross-sectional studies, retrospective and prospective cohort studies, randomized controlled trials (RCTs), and clinical trials. Exclusion criteria were as follows: (1) Article types such as editorials, letters, comments, reviews, meta-analyses, study protocols, abstracts or reports for conferences, expert opinions, technical notes, etc.; (2) case reports or case series (up to five patients); (3) animal or in vitro experimental studies; (4) studies with a partially overlapping patient cohort. For studies with an overlapping study population, the study with the largest population was selected. The inclusion and exclusion criteria were defined a priori.

Data extraction

Year of publication, study design, country location, first author, demographic data of patients, number of

patients, types of gliomas, dose and course of temozolomide, and seizure outcomes were extracted from each article. Two independent authors assessed all titles, abstracts, and full texts for eligibility. If a discrepancy was present, the team leader was consulted to reach a consensus.

Quality assessment and evidence grading

The quality of each eligible study was assessed independently and in duplicate by two of the authors by using the Oxford Centre for Evidence-Based Medicine (OCEBM) hierarchy. This classification prioritizes evidence at levels ranging from 1 to 5, level 5 being the "least good" and level 1 being the "best evidence." Levels 1, 2, 3, 4, and 5 indicate high-quality and well-designed RCTs, retrospective and prospective cohort studies, case-control studies, case-series and cross-sectional studies, and expert opinion or unpublished clinical observations, respectively. Discrepancies were settled by consensus among the research team.

Results

Search results and study characteristics

The flow diagram of record analysis and study inclusion is displayed in [Figure 1]. The initial electronic database search yielded 178 total records, of which 18 duplicates were deleted by manual screening in EndNote X9, identifying 160 English articles for the title and abstract screening published between 2003 and 2021. According to our exclusion criteria, 28 studies qualified for full-text evaluation, and a further 19 articles were excluded for the following reasons: one article with partially overlapping patients, two articles with less than five patients, four articles did not report the outcome of seizure in glioma patients after TMZ treatment, one editorial commentary and three review papers, and eight articles that were not in the field of interest. Finally, nine original studies were suitable for inclusion in qualitative analysis, of which four were prospective phase II studies,[18],[19],[25],[26] one was a randomized controlled trial,[27] and four were retrospective case series.[23],[28],[29],[30] Studies were spread globally, with most conducted in Europe and North America. Three studies were from Italy,[19],[25],[26] two from America,[23],[29] one from the UK,[18] one from the Netherlands,[28] one from China,[30] and one from Canada, Australia, Belgium, etc.[27] There were five single-center studies[18],[19],[23],[29],[30] and four multicenter studies.[25],[26],[27],[28] The collective time period of data examined was over 22 years with publication years spanning 2003 to 2020. Of the included studies, the quality of evidence (OCEBM) from seven studies was graded as level 4[18],[19],[25],[26],[28],[29],[30] and two studies were graded as level 2.[23],[27]{Figure 1}

All studies consisted of 91 patients with astrocytoma or diffuse astrocytoma IDH-mutant/wild type, 117 with oligodendroglioma or oligodendroglioma IDH-mutant 1p19q codeletion, 24 with oligoastrocytoma, and 281 with glioblastoma. In addition, Pace A, Sherman JH, and Jiang H recorded 31, 5, and 12 LGGs patients without detailed classification, respectively.[19],[23],[30] Gliomas were common in frontal, temporal, and parietal lobes. Most of the patients had undergone biopsy or surgical resection, except for four articles that did not record the surgical procedures.[19],[25],[26],[30] Study characteristics are summarized in [Table 1], [Table 2], and [Table 3].{Table 1}{Table 2}{Table 3}

TMZ treatment and seizure outcome

[Table 4] details the treatment schedule for TMZ in each study; 150–200 mg/m2/day for 5 consecutive days of a 28-day cycle for up to 12 cycles or until disease progression was the standard regime of TMZ chemotherapy adopted in several studies.[18],[19],[27] Among them, Pace et al.[19] reported that the dose of TMZ in PCV (procarbazine, lomustine, and vincristine) pretreated patients was 150 mg/m2/day, and the dose increased to 200 mg/m2/day without toxicity. Villani et al.[25] applied a low dose of TMZ (50 mg/m2/day) given 1 week on/1 week off until disease progression or for a maximum of 24 months. Additionally, 150 mg/m2/day 1 week on/1 week off every 4 weeks up to a maximum of 18 cycles was the treatment plan of TMZ used in one study.[26] Unfortunately, the treatment protocol for TMZ was not described in detail in four studies.[23],[28],[29],[30] Indeed, it should be noted that the dose and cycle of TMZ in each study were not fixed but were adjusted according to the response of patients. [Table 4] summarizes seizure outcomes after treatment with

TMZ. Seven case series studies have shown that TMZ can alleviate epileptic seizures in patients with LGGs. In five of these studies, the proportion of patients with reduced seizure frequency after TMZ chemotherapy was 54%,[18] 29%,[19] 57.1%,[25] 89.7%,[29] and 87%,[26] respectively. In four of these studies, the proportion of patients with seizure-free after TMZ chemotherapy was 21%,[18] 19.4%,[19] 28.6%,[25] and 72%,[26] respectively. Koekkoek et al.[28] found that at 6, 12, and 18 months after TMZ treatment, 49.0%, 63.2%, and 61.8% patients showed a ≥50% seizure reduction, respectively. Moreover, Jiang et al.[30] reported that adjuvant chemotherapy with TMZ was related to a better postoperative seizure outcome. The results of a retrospective cohort study showed that the frequency of seizures in patients with LGGs treated with TMZ was significantly lower than that of patients without TMZ. In addition, seven patients (18%) in the TMZ group showed this amelioration independent of antiepileptic drug (AED) adjustment compared with no patient in the control group.[23] In a multicenter RCT of elderly patients with glioblastoma, TMZ plus short-course radiotherapy has no obvious antiepileptic benefit compared with radiotherapy alone.[27]{Table 4}

Discussion

We completed a thorough search of two major databases and discreetly reviewed the articles that met the eligibility criteria. The present systematic review on seizure outcomes in patients with gliomas who received TMZ yielded nine studies from multiple research institutions with records that span from 1998 to 2019 and a geographical scope concentrated in Europe, North America, and Asia.

Seizures may be the earliest and only clinical symptom of gliomas in clinical practice.[3],[4],[5],[6],[7],[8],[9] In addition to being a prognostic indicator of successful anti-tumor therapy, seizure remission in itself means a clinical benefit for the patients with gliomas as it may contribute to an improved quality of life and better cognitive function.[6],[31],[32],[33] Apart from treatment with various AEDs, appropriate and timely anti-tumor or antineoplastic therapies, such as resection surgery, PCV chemotherapy, and radiotherapy, may contribute to a reduction in seizure frequency.[12],[34],[35],[36] For instance, postoperative radiotherapy has been demonstrated to improve seizure control in patients with grade II and III gliomas.[37] Participants with LGGs who underwent early postoperative radiotherapy had better seizure control at 1 year than participants who underwent delayed radiation.[38] Complete excision is a good predictor of seizure freedom in glioma, and the extent of resection relates to seizure freedom. For people with LGGs who suffer epileptic seizures, Xu et al.[39] propose that seizure freedom can be achieved when the extent of resection is more than 80%. Shifting our focus to the role of TMZ in gliomas-related seizures, from the several case series studies on LGGs we included, the percentage of patients with partial seizure control after TMZ treatment ranged from 29% to 89.7%, and the percentage of patients with complete seizure control or seizure-free after TMZ treatment ranged from 19.4% to 72%. In view of the descriptive nature of these studies and the absence of a control group (non-TMZ treatment group), there were significant differences in the rates of epileptic remission after TMZ treatment in different studies. In a retrospective cohort study of 69 patients with LGGs, there was a marked difference in decreased seizure frequency between patients receiving TMZ (n = 23, 23/39) and those who did not receive TMZ (n = 4, 4/30; $P < 0.001$). According to our assessment, the evidence level of the above study is level 2; thus, the message of the study is clear: postoperative TMZ chemotherapy is associated with a favorable seizure outcome. Similarly, Jiang et al. came to the same conclusion.

Little is known about tumor-related seizure control in glioblastoma. Given that TMZ is the most effective cytotoxic drug against glioblastoma and that the standard dosing of TMZ has shown a good safety profile in clinical practice, TMZ should reduce seizure frequency to some extent. However, in a multicenter randomized trial, TMZ seemed to have little effect on tumor-related seizure control in elderly patients with glioblastoma (radiotherapy alone group vs. radiotherapy plus TMZ group, $P = 0.15$). Additionally, elderly patients with glioblastoma receiving radiotherapy alone tended to suffer seizures earlier than those receiving radiotherapy plus TMZ, but the difference was not statistically significant ($P = 0.054$). It should be noted that this study is not a well-designed randomized controlled trial due to the lack of information on the history of epilepsy, EEG data, and antiepileptic drug use. Thus, the evidence level of this study is level 2.

The mechanism of action in how TMZ shows this antiepileptic effect is unclear. So far, no independent mechanism of TMZ's antiepileptic effect has been reported. We speculate that TMZ may be exerting its effect

by killing glioma cells that may be actively irritating surrounding neurons or altering the peritumoral microenvironment to trigger seizures. Therefore, compared with traditional antiepileptic drugs, the onset time of the antiepileptic effect of TMZ may be longer. Unfortunately, there are no studies and hypotheses on the duration of the antiepileptic effect of TMZ.

Several limitations to this review are of note. Narrative review is the nature of this paper. After strict and meticulous literature screening, a total of nine articles were collected. Therefore, readers should consider the weakness of the small sample size in this paper when interpreting and applying the results. The second drawback concerns article selection: only papers in English were included, although the authors are aware that effective and consistent literature on this subject has also been published in Chinese, German, Spanish, and French. For this reason, there is a possibility that some data are missed in this review. Seven retrospective or prospective case series studies were graded level 4 quality, and two retrospective cohort or RCT studies were graded level 2. Thus, the quality of the studies was medium or low level. Finally, different institutions adopt different TMZ treatment schedules, which makes it impossible for us to conduct quantitative analysis on the included studies.

Conclusion

To our knowledge, this is a novel systematic literature review to investigate the potential link between TMZ chemotherapy and seizures in different grades of gliomas. As current evidence of TMZ alleviating gliomas-associated seizures is not sufficient, further studies are needed to clarify whether TMZ can bring substantial clinical benefits to patients with gliomas-associated seizures. The original intention of TMZ chemotherapy is to inhibit the malignant growth of glioma cells. If there is an additional antiepileptic effect, it should be adopted without hesitation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Figure 1: Flow diagram of record analysis and article inclusion

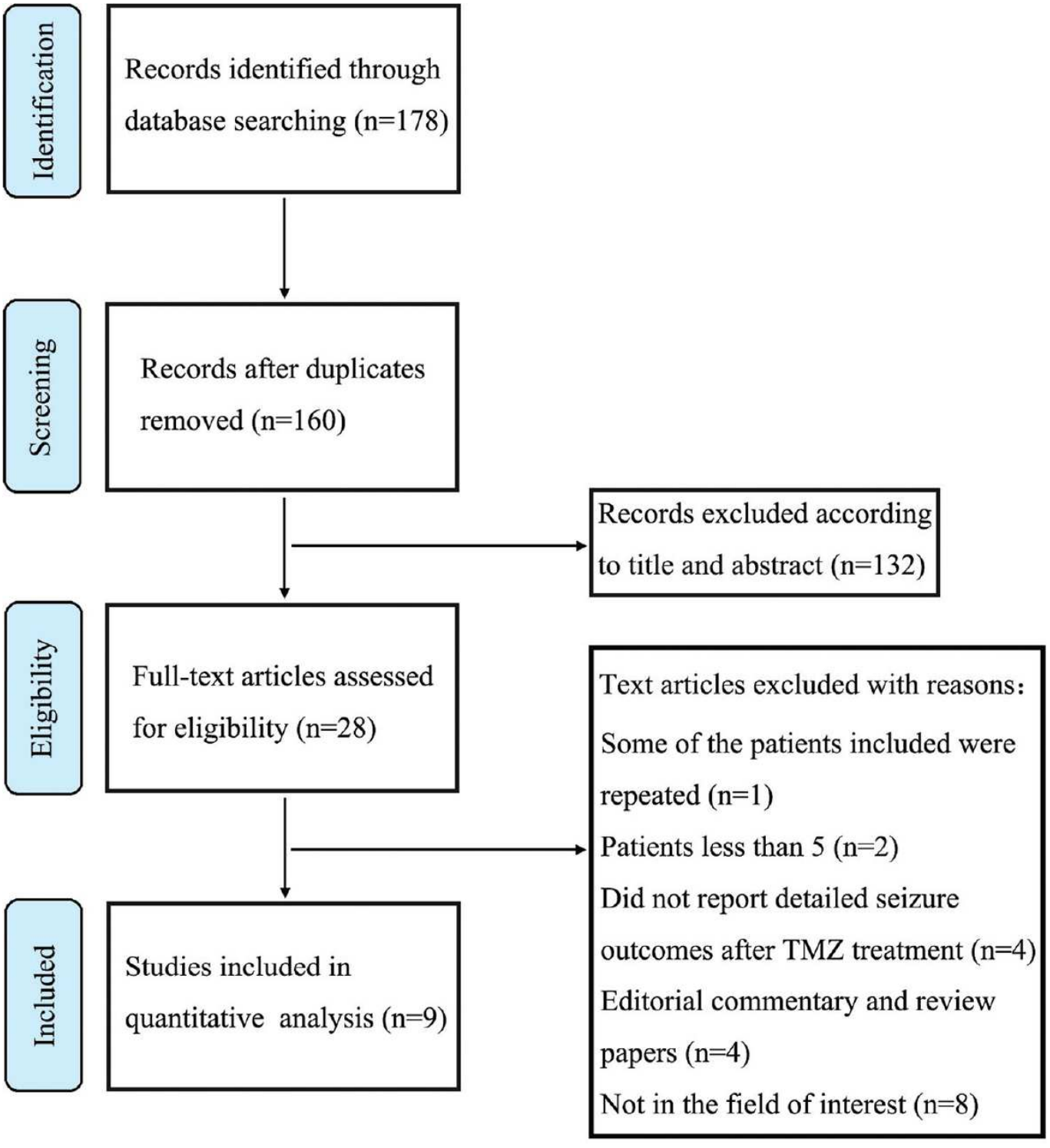

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Table 1: Summary of studies included in this review

Author and Year	Country	Time period	Study design	Center (s)	OCEBM level of evidence
Brada M, 2003[18]	UK	March 1998-March 2000	Prospective phase II case series	Single	4
Pace A, 2003[19]	Italy	April 2000-September 2002	Prospective phase II case series	Single	4
Sherman JH, 2011[23]	USA	2002-2007	Retrospective cohort study	Single	2
Koekkoek JA, 2016[28]	Netherlands	January 2002-January 2014	Retrospective case series	Multicenter	4
Villani V, 2017[25]	Italy	2006-2009	Prospective phase II case series	Multicenter	4
Haggiagi A, 2018[29]	USA	2005-2015	Retrospective case series	Single	4
Jiang H, 2019[30]	China	January 1, 2015-July 31, 2019	Retrospective case series	Single	4
Rudà R, 2019[26]	Italy	April 2007-December 2010	Prospective phase II case series	Multicenter	4
Climans SA, 2020[27]	Canada, Australia, etc.	November 2007-September 2013	Randomized controlled trial	Multicenter	2

OCEBM, Oxford Centre for Evidence-Based Medicine

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Table 2: Basic findings and patient characteristics of the selected studies

Author and Year	No. of patients treated with TMZ (Male/Female)	Age (years)	Glioma classification (s)	Tumor location	Operative methods
Brada M, 2003[16]	30 (13/17)	40 (25-68)	Astrocytoma, 17 Oligodendroglioma, 11 Mixed oligoastrocytoma, 2	Frontal, 11 Temporal, 5 Parietal, 2 Fronto-temporal, 4 Fronto-parietal, 4 Other, 4	Biopsy alone, 18 Surgical resection, 12
Pace A, 2003[19]	31	Unclear	LGGs (the detailed classification is unclear)	Unclear	Unclear
Sherman JH, 2011[23]	39 (23/16)	46 (26-74)	Astrocytoma, 3 Oligodendroglioma, 22 Oligoastrocytoma, 11 LGG NOS, 3	Frontal, 22 Temporal, 2 Parietal, 5 Frontotemporal, 6 Frontoparietal, 2 Temporooccipital, 1 Diffuse hemispheric, 1	Biopsy, 24 Resection, 14 Not recorded, 1
Koekkoek JA, 2016[28]	53 (28/25)	47.3	Astrocytoma, 32 Oligoastrocytoma, 7 Oligodendroglioma, 14	Frontal, 29 Temporal, 11 Parietal, 7 Occipital, 1 Basal ganglia/midline, 5	Gross-total resection, 5 Partial resection, 25 Biopsy, 23
Villani V, 2017[25]	14 (9/6)	44 (19-77)	Astrocytoma, 8 Oligodendroglioma, 2 Oligo-astrocytoma, 4	Unclear	Unclear
Haggiagi A, 2018[29]	39 (24/15)	41 (22-62)	Oligodendroglioma	Frontal, 25 Temporal, 6 Parietal, 4 Occipital, 2 Basal ganglia, 1 Diffuse hemispheric, 1	Gross total resection, 18 Subtotal resection, 10 Biopsy, 11
Jiang H, 2019[30]	33	Unclear	LGGs (the detailed classification is unclear)	Unclear	Unclear
Rudà R, 2019[26]	60 (36/24)	51.5 (39.5-65.0)	Oligodendroglioma IDH^{mt} 1p19q cod, 29 Diffuse astrocytoma IDH^{mt}, 9 Diffuse astrocytoma IDH^{wt}, 22	Frontal lobe, 28 Temporal lobe, 15 Fronto-temporal lobe, 15 Parietal lobe, 2	Unclear
Climans SA, 2020[27]	281 (171/110)	≥65	Glioblastoma	Unclear	Biopsy only, 89 Partial or complete resection, 192

NOS, not otherwise specified; IDH, isocitrate dehydrogenase

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Table 3: Seizure characteristics

Author and Year	Seizure type	Seizure frequency	Seizure duration	AEDs
Brada M, 2003[18]	Unclear	Unclear	Unclear	Unclear
Pace A, 2003[19]	Unclear	Unclear	Unclear	Unclear
Sherman JH, 2011[23]	Unclear	Unclear	Unclear	Monotherapy, 14 (36)
				Polytherapy, 25 (64)
Koekkoek JA, 2016[28]	Partial simple, 23 (43.4)	≥1/week, 22 (41.5)	Unclear	Polytherapy, 34 (64.2)
	Partial complex, 7 (13.2)	<1/week, 31 (58.5)		
	Secondary generalized, 15 (28.3)			
	Both partial and generalized, 8 (15.1)			
Villani V, 2017[25]	Unclear	Unclear	Unclear	Unclear
Haggiagi A, 2018[29]	Simple partial, 7 (18)	Daily, 9 (23)	Unclear	Monotherapy, 18 (46)
	Complex partial, 10 (25.6)	≥1 per week, 12 (30.8)		Polytherapy, 21 (54)
	Simple and complex partial, 7 (18)	<1 per week, 18 (46.2)		
	Partial and generalized, 14 (35.8)			
	Generalized, 1 (2.6)			
Jiang H, 2019[30]	Unclear	Unclear	Unclear	Unclear
Rudà R, 2019[26]	Partial simple, 18 (46.2)	Daily, 18 (46.2)	Unclear	Monotherapy, 17 (43.6)
	Partial complex, 17 (43.6)	Weekly, 12 (30.8)		Polytherapy, 20 (51.3)
	Secondary generalized, 4 (10.3)	Monthly, 9 (23.1)		
Climans SA, 2020[27]	Unclear	Unclear	Unclear	Unclear

AED, Antiepileptic drug

NEUROLOGY INDIA
Publication of the Neurological Society of India

Table 4: TMZ treatment plan and seizure outcomes after TMZ treatment

Author and Year	TMZ treatment schedule	Seizure outcome
Brada M, 2003[18]	200 mg/m²/day for 5 days, on a 28-day cycle, for a maximum of 12 cycles or until tumor progression. Twenty four patients received 12 cycles of chemotherapy.	Fifteen of 28 patients (54%) with epilepsy had reduction in seizure frequency, of whom 6 (21%) became seizure-free.
Pace A, 2003[19]	200 mg/m²/day for 5 days, on a 28-day cycle if not pretreated, or 150 mg/m²/day in PCV pretreated patients, with dose escalation to 200 mg/m²/day in the absence of toxicity. TMZ was administered for a median of 10 cycles (range: 3-22); a total of 469 cycles was performed.	Complete seizure control was obtained in 6 patients (19.4%) and partial seizure control in 9 patients (29%) treated with TMZ.
Sherman JH, 2011[23]	The dose of TMZ is not clear. TMZ treatment cycle were assessed at each neuro-oncology clinic visit.	Four patients (13%) in the control cohort demonstrated a greater than 50% reduction in seizure frequency; however, in the TMZ cohort, 23 patients (59%) showed a greater than 50% decrease in seizure frequency (P<0.001). Seven patients (18%) in the TMZ group showed this amelioration independent of AED adjustment compared with no patient in the controls.
Koekkoek JA, 2016[28]	The dose of TMZ is not clear. At least 6 cycles, or until renewed tumor progression or unacceptable toxicity emerged.	Six, 12 and 18 months after TMZ treatment, 49.0% (25/51), 63.2% (24/38), and 61.8% (21/34) patients showed a ≥50% seizure reduction, respectively. There were no significant differences between patients with and without a ≥50% seizure reduction at 6, 12, and 18 months after TMZ treatment.
Villani V, 2017[25]	50 mg/m²/day 1 week on/1 week off until progression or for a maximum of 24 months. 18 cycles (mean) per patient (range 3-24 cycles).	Two (28.6%) patients were seizure-free, four (57.1%) patients Showed a reduction of epileptic seizures, and one (14.3%) showed stable frequency of seizures.
Haggiagi A, 2018[29]	Unclear	Reduction in seizure frequency occurred in 35 patients (89.7%). Improvement was independent of AED regimen adjustments or prior antitumor treatment in 16 (41%); of these the AED dosage was successfully reduced or completely eliminated in 10 patients (25.6%) at the end of TMZ treatment.
Jiang H, 2019[30]	Unclear	Univariate analysis showed that adjuvant chemotherapy with TMZ (x^2=4.081, P=0.043) were associated with postoperative short-term seizure outcome.
Rudà R, 2019[26]	150 mg/m²/day 7 days-on/7 days-off every 28 days up to a maximum of 18 cycles. Median number of TMZ cycles was 11 (range 7-18). In 31 patients (51.7%) the daily dose of TMZ was decreased from 150 to 100-130 mg/m² following a median number of 4 cycles (range: 2-9) due to persistent myelotoxicity, thus reducing the dose intensity.	A reduction of seizure frequency>50% was observed in 87% of patients and seizure freedom in 72%.
Climans SA, 2020[27]	150-200 mg/m²/day for 5 consecutive days of a 28-day cycle for up to 12 cycles or until disease progression.	In the radiotherapy alone group, 68 patients (24%) had a documented or self-reported seizure versus 83 patients (30%) in the TMZ plus radiotherapy group, Chi-square analysis showed no difference.

PCV, procarbazine, lomustine, and vincristine; AED, Antiepileptic drug