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Temozolomide as Treatment in Low-grade Glioma: A Systematic Review

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Abstract

Background: With the advent of newer chemotherapeutic agents, the use of Temozolomide is becoming an option in the treatment of low-grade glioma (LGG). This systematic review aims to look into the available evidences on the efficacy of Temozolomide in the management of LGG and determine if it is a good and reasonable option for the patients.

Method: A literature search and systematic review was conducted primarily answering the question: "What is the efficacy of Temozolomide in the treatment of LGG?" A two-phase abstraction was utilized yielding a total of nine studies included in thereview.

Results: Ten prospective single-arm studies were initially included but one study was adjudicated as having low quality. Nine studies involving 453 patients with LGG were included. In this review, the three-year overall survival of patients diagnosed with LGG who were given Temozolomide were noted to be high ranging from 73.1-82.0% while progression-free survival showed a wide variation across studies ranging from 11.0-98.0%. Reduction in seizure frequency was seen in 48-62% of the patients. The occurrence of mild to moderate hematologic toxicity is quite common at 10-97%.

Conclusion: We conclude that Temozolomide showed consistently high overall survival and reduction in seizure frequency among patients diagnosed with LGG. Variable responses on objective radiologic response, quality of life and progression-free survival rates were noted. Future studies should look into the efficacy of Temozolomide as an adjunct or as an initial treatment in LGG with a comparison with a control group in order for more conclusions to be made.

Keywords: Temozolomide; Low-grade glioma; Chemotherapy

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Introduction

Low-grade gliomas (LGG) comprise a diverse group of tumors arising from the glia. The glial cells, which support the central nervous system may give rise to the common LGG such as astrocytomas, oligodendrogliomas and oligoastrocytomas, which are technically classified under Grade I and II in the World Health Organization criteria. LGG accounts for 40% of all the primary brain tumors. The treatment of low- grade glioma has long been one of the most controversial because of the indolent nature of the disease and the absence of well-designed clinical trials [1-3]. It has been a widely acceptable practice to do watchful waiting in patients diagnosed with LGG since they are relatively younger with no neurologic deficits. However, this was refuted because of recent studies suggesting its malignant potential if left untreated [4]. Since then, the management of LGG has been changing and dynamic. In the Radiation Therapy Oncology Group (RTOG) data, postoperative radiotherapy and chemotherapy leads to longer survival in patients with LGG [5]. Despite this finding, there is still no consensus in the treatment of LGG and physicians tend to have different approaches to the disease [6]. In a recent study by Field et al., they found variable management of LGG among physicians with significant gap on the "ideal world" from the "real world" management. Also, it was an interesting finding that Temozolomide is the chemotherapy of choice among the physicians despite its novelty and some evidences pointing to its

hypermutable capacity and propensity for the tumor to rapidly progress [7,8].

Temozolomide is becoming a chemotherapeutic option in patients diagnosed with LGG. Although it is only approved in the treatment of anaplastic astrocytoma and newly diagnosed glioblastoma, it is becoming popular in the treatment of LGG because of its oral administration and favorable toxicity profile compared to other chemotherapy such as Procarbazine, Lomustine and Vincristine (PCV), which is the standard chemotherapy regimen in LGG [9,10]. Although it is usually given after postoperative radiotherapy, some uses it as upfront treatment after diagnosis with favorable results in retrospective studies [11,12]. Therefore, the aim of this systematic review is to summarize, critically appraise and quantify the findings of randomized and non-randomized controlled trials of Temozolomide as first-line and second-line treatment in LGG.

Methodology

We conducted this systematic review following the Cochrane Handbook for Systematic Reviews and reported the findings according to the Preferred Reporting Items for Systematic Review and Metaanalysis (PRISMA) [13].

Populations, interventions, comparators and study designs

The primary research question was "What is the efficacy of Temozolomide in the treatment of low-grade glioma?" Studies fulfilling the following criteria were included in this study: 1) randomized and non-randomized trial conducted in any setting, 2) published in the English language, 3) conducted in patients diagnosed with low-grade glioma by histopathology including supratentorial astrocytoma, oligodendroglioma and mixed oligoastrocytoma, and 4) patients aged 18-60 years old. Studies done earlier than 1990 were excluded.

Search strategy

We searched the following databases for randomized and non-randomized controlled trials: Medline, EMBASE, Cochrane Central Register for Controlled Trials, CINAHL, Clinicaltrials.gov and Scopus using the following search terms: low-grade glioma, oligodendroglioma, astrocytoma, oligoastrocytoma, LGG, low-grade brain tumor, Temozolomide and chemotherapy.

Study selection

The screened titles and abstracts were screened in two phases using EPPI- Reviewer 4. In the first phase, titles and abstracts were reviewed to ensure that the study was conducted in a patient diagnosed with low-grade glioma using Temozolomide as one of the interventions. The second phase was done primarily to determine which were the clinical trials. The full articles of the studies obtained from the two-phase abstraction were reviewed.

Risk of bias assessment

The reviewers assessed the internal validity of the included studies using the Risk of Bias in non-randomized studies of intervention (ROBIN-I) tool developed by the Cochrane Bias Methods Group [14,15]. The strength of evidence was also evaluated using the approach developed by the Grade Working group [16].

Data abstraction

The reviewers extracted data from the included studies using the EPPI- Reviewer 4 program. The following information were extracted: characteristics of the patient population, histopathology, functional status, molecular signature using the 1p/19q and O6-methylguanine methyltransferase (MGMT) methylation status, previous treatment received, intervention dosing and frequency, overall survival (OS), progression-free survival (PFS), imaging characteristics, neurological improvement and toxicity profile.

Data synthesis and analysis

The data extracted were summarized using descriptive statistics, which includes the mean, median and range of values. The study findings were tabulated for inter-study comparison. The overall survival and the progression-free survival across the included studies were compared. The secondary outcomes, which were the objective imaging response, improvement in the quality of life, improvement in neurologic symptoms and the experienced adverse events weredetermined.

Results

Study search results

A total of 688 articles were reviewed, excluding 410 articles during the first phase of screening. More than 60% (259/410) were excluded because these studies were not solely on low-grade glioma while around 10% (51/410) were on pediatric patients and approximately 30% (100/410) were not using Temozolomide as an intervention. In the second phase of the screening, 90% (254/278) were excluded because the studies were not clinical trials. The reviewers looked on the full-text manuscripts of the 24 remaining articles. However, 14 articles were excluded because five of the articles had no full-text manuscript available despite direct correspondence with the authors, four articles were on spinal cord and five articles includes Grade III/IV gliomas. A total of 10 articles were deemed relevant to this study **(Figure 1).**

Risk of bias assessment

All the included studies were prospective non-randomized single-arm clinical trials. No randomized controlled trial was available during the time the reviewers performed this study. This is the reason why the reviewers decided to use the recently developed ROBIN-I tool, which is particularly designed to evaluate non-randomized trials [15]. The studies were individually evaluated on its potential for selection bias, intervention bias, outcome measurement bias, attrition bias and selective reporting bias (Appendix A). One clinical trial was excluded during the assessment process because the outcome measure was deemed to be subjective and the beginning of the intervention and the follow-up did not coincide among the patients included. Also, there was no mention of the drop-out participants in the study [10].

Level of evidence

For the objective outcomes on the efficacy of Temozolomide, the quality of evidence of the nine remaining studies was evaluated

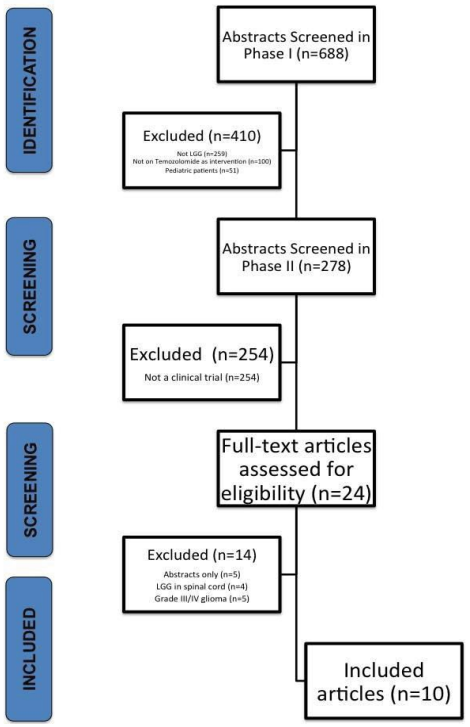

Figure 1 Study Flow Diagram.

using the GRADE assessment. The quality of evidence of all the studies was deemed to be of moderate strength (Appendix B).

Description of the included studies

Table 1 summarizes the characteristics and findings of the included studies. The nine studies were published in 2001-2015 and were conducted in the United Kingdom (n=1) [17], United States (n=3) [18-20], France (n=1) [21], Italy (n=2) [22,23] and Belgium (n=2) [24,25]. The number of subjects involved ranged from 30 to 129 patients with LGG (Total=453 patients). All patients included underwent surgery and/or either radiotherapy or chemotherapy. All the studies looked into the survival rates, either the overall survival or the progression-free survival. Seven studies looked into the objective imaging response of Temozolomide on LGG [17,19,20-24] while three studies also looked on improvement in neurological function [21-23]. Only two studies looked into the quality of life [17,22].

Intervention

Temozolomide was given in a variety of ways across the different studies. In seven of the nine studies, it was given orally daily for five consecutive days in a 28-day cycle for 12-24 cycles as long as the side effects are acceptable to the patient [17,18,20-25]. In two studies, it was given at a lower dose of 75 mg/m^2 but for a longer duration of 21-49 days [19,23].

Primary outcome

One of the studies, the study of Fisher et al. was initially designed as a randomized controlled trial but was amended to a single-arm clinical trial because of the difficulty of patient accrual. In this study, the investigators used a historical control to analyze the results of Temozolomide in patients with LGG. An overall survival of 54% is set among the control group and a 20% improvement in the three-year overall survival is required for a result of a trial to be significant.18 In this review, the three-year overall survival of patients diagnosed with LGG who were given Temozolomide were noted to be high ranging from 73.1% to 82.0%, which is better than the 20% improvement using the historical control [17-19]. On the other hand, the results of the PFS rates showed wide variation ranging from 11% to 98%. The lowest progression-free survival rates were seen among those patients who failed after surgery, radiotherapy and chemotherapy with PCV.25

Secondary outcomes

Only two studies looked into the improvement in the quality of life. One study used the health-related quality of life domains using functional scales on the physical, social, emotional and cognitive aspects. Of the 28 evaluable patients, it was noted that 96% had an improvement in at least one of the domains after using Temozolomide, and this was notable in patients who also had improvement in the size of the lesion as seen in serial imaging [17]. In another study, the QLQ-C30 questionnaire developed by the European Organisation for Research and Treatment of Cancer was utilized. An improvement in the quality of life parameters were similarly seen more frequently in patients with more marked imaging response [22]. Improvement in neurologic deficit was mainly determined by the reduction in seizure frequency as shown in three of the included studies. The improvement was consistently defined as >50% reduction in seizure frequency without modification of steroid and antiepileptic drug dose and it was seen in 48-62% of the patients [21-23].

The objective radiologic response through serial magnetic resonance imaging was also determined in seven studies. Favorable response are those categorized as complete response with complete disappearance of the lesion and those with partial response with >50% reduction in the size of the lesion. Complete response was only seen in three studies and comprising 9.3% to 26.3% of patients within two to six months of follow-up [20,22,24]. Partial response was more frequently seen ranging from 10.3% to 38.6% of patients. On the other hand, Temozolomide may not be very beneficial if it was categorized under mild response with only 25-50% reduction in the lesion or progressive disease having >25% increase in the size of the lesion or stable disease having <25% increase or decrease in the size of the lesion **(Table 1).**

Side effects

In patients receiving chemotherapy, the National Cancer Institute published a standardized way to assess the adverse events. Adverse events are graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3) or life- threatening (Grade 4) depending on specific parameters in every organ system [26]. In this review, the occurrence of mild to moderate hematologic toxicity is quite common at 10% to 97% manifesting as neutropenia, lymphopenia or thrombocytopenia. There is also a small prevalence of patients presenting with nausea, vomiting, infection and metabolic derangements.

Table 1 Summary Table of the Included Studies.

	Patient population	Histopathology	KPS score	1p/19q status	MGMT methylation	Previous treatment	Temozolomide dose/ frequency/ duration	OS	PFS	QOL	Improvement in Neurological deficit	Imaging response	Adverse Events
Brada	30 patients aged 25-68 yo (Median age: 40 yo)	A=17, O=11, OA=2	60-100	NI	NI	Surgery	200 mg/m^2 orally daily for 5 days given every 28 days for 12 cycles	2-yr: 87% 3-yr: 82%	2-yr: 76% 3-yr: 66%	96% improvement in at least 1 HQOL domain	NI	PR=3, MR=14, SD=11, PD=1	6 with Grade 3/4 hematologic toxicity, 2 with Grade 3 constipation, 1 with Grade 3 nausea and vomiting
Fisher	129 patients aged 20-76 yo (Median age: 49 yo)	A=71, O=29, OA=29	70-100	NI	NI	Surgery, RT	Concurrent 75 mg/m^2 orally daily during RT and up to 12 cycles of adjuvant 150-200 mg/m^2 daily for 5 days every 28 days	3-yr: 73.1% (95% CI 65.3-80.8) 5-yr: 57.1% (95% CI 47.7-66.5)	3-yr: 59.2% (95% CI 50.7-67.8)	NI	NI	NI	42.6% experienced Grade 3 adverse events, 10.1% experienced Grade 4 adverse events
Hong-Xuan	60 patients aged 24-72 yo (Median age: 43 yo)	O=49, OA=11	40-100	12/26 tested with LOH	NI	Surgery	200 mg/m^2 orally daily for 5 days given every 28 days for 12-24 cycles	NI	1-yr: 73%	NI	30 with reduction in seizure frequency	PR=10, MR=8, SD=36, PD=5	5 (8%) developed Grade 3/4 hematologic toxicity
Kesari	44 patients aged 20-68 yo (Median age: 43 yo)	A=6, O=26, OA=12	70-100	1p deleted=21, 19q deleted=19, codeleted=18	12/26 of those tested are positive for methylation	Surgery + RT in 12 patients	75 mg/m^2 orally daily for 49 days followed by 28 days off for 6 cycles	1-yr: 98% 3-yr: 81% 5-yr: 73%	1-yr: 91% 3-yr: 57% 5-yr: 34%	NI	NI	PR=9, SD=33, PD=2	38 had Grade 2 hematologic toxicity, 5 had Grade 3/4 hematologic toxicity, 1 had Grade 2 nausea
Pace	43 patients aged 21-69 yo (Median age: 39.5 yo)	A=29, O=4, OA=10	70-100	NI	NI	Surgery + RT in 30 patients and PCV chemo in 16 patients	200 mg/m^2 orally daily for 5 days every 4 weeks if not pre-treated with PCV, 150 mg/m^2 if with previous PCV treatment for 4-12 cycles	NI	6-mos: 76% 1-yr: 39%	13 improved, 15 stable using the QLQ-C30 questionnaire	15/31 with reduction in seizure frequency	CR=4, PR=16, SD=17, PD=6	9 had Grade 3 hematologic toxicity, 1 had gastrointestinal toxicity

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Quinn	46 patients (Median age: 41 yo)	A=21, O=20, OA=5	70-100	NI	NI	Surgery + RT in 7 patients and Chemo in 12 patients	200 mg/m^2 orally daily for 5 days given every 28 days for 12 cycles	NI	6-mos: 98% (95% CI 94-100) 12-mos: 76% (95% CI 63-42)	NI	NI	CR=11, PR=17, SD=16	5 had Grade 3 hematologic toxicity
Tosoni	30 patients aged 24-69 yo (Mean age: 45 yo)	A=9, O=18, OA=3	60-90	21 (70%) with 1p/19q LOH	14 (46.7%) are positive for methylation	Surgery	75 mg/m^2 orally daily for 21 days given every 28 days for 12 cycles	1-yr: 97% (95% CI 91-100) 2-yr: 79% (95% CI 65-96)	1-yr: 73% (95% CI 59-91) 2-yr: 43% (95% CI 28-65)	NI	475 had overall neurologic improvement, 62% with reduction in seizures	PR=9, SD=17, PD=4	31% had thrombocytopenia, 18% had lymphopenia, 37.5% with leucopenia, 12% had infection
Van den Bent 26971	39 patients aged 20-64 yo (Median age: 48.6 yo)	O=24, OA=15	40-100	NI	NI	Surgery + RT	200 mg/m^2 orally daily for 5 days given every 28 days for 12 cycles	NI	6-mos: 71% 1-yr: 40%	NI	NI	CR=10, PR=10, SD=12, PD=6	10 had Grade 3/4 hematologic toxicity
Van den Bent 6972	32 patients aged 27-56 yo (Median age: 43.6 yo)	A=4, O=17, OA=11	40-100	NI	NI	Surgery + RT and chemo with PCV	150 mg/m^2 orally daily for 5 days given every 28 days for 12 cycles	NI	6-mos: 29% 1-yr: 11%	NI	NI	NI	2 had Grade 3 hematologic toxicity

*KPS – Karnofsky Performance Scale; MGMT - O6-methylguanine-methyltransferase; OS – overall survival; PFS – progression-free survival; QOL – quality of life; NI – no information available; A – astrocytoma; O – Oligodendroglioma; OA – oligoastrocytoma; RT – radiotherapy; LOH – loss of heterozygosity; CR – complete response; PR – partial response; MR – mild response; SD – stable disease; PD – progressive disease

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Discussion

This study aims to review the available evidences on the use of Temozolomide in low-grade glioma. A difference in the Temozolomide dosing was seen in this review. The reason behind protracted Temozolomide dosing is to increase Temozolomide dose density and at the same time decrease the related adverse events. It may also result in depletion of MGMT proteins leading to more sensitivity to Temozolomide [19]. MGMT was found to encode DNA repair protein which can revert the alkylating effect of Temozolomide, hence repairing the damaged cells. By prolonging the exposure to Temozolomide, it was suggested that these proteins become saturated and eventually inactivated making Temozolomide effective [23]. In the same way that MGMT status is an important prognostic factor in the response of LGG, the loss of heterozygosity of chromosome 1p and 19q also showed a significant association in the effectiveness of the chemotherapy [21]. Although not all the studies included in this review determined the status of these factors, its use in future studies may be an important inclusion.

Variable responses on radiologic effects, quality of life and progression-free survival rates were noted. Across studies, the overall survival has consistently improved in majority of the patients but the progression-free survival showed inconclusive results. This is in contrast with other clinical trials where PFS usually improve more than the OS because it was postulated that the degree of improvement set by most clinical trials was most of the time insufficient to translate to OS improvement [27]. This may be attributed to the heterogeneity of the patients since most patients only underwent previous surgery but some already received combination therapy. Although the reviewers find it helpful to have a metaanalysis be done, the absence of a control and the difference in time interval in measuring the PFS makes it impossible in this review.

Quality of life became one of the most common measures in clinical trials especially that it tries to measure the perceived satisfaction of patients [27]. However, in this review, only two studies utilized it. This is probably due to the subjective nature of the questionnaire. Also, it was found that most of the tools to measure QOL had minimal change despite significant improvements, making some adjustments necessary [28]. In this review, the improvement in neurologic deficit was limited to the measurement of the reduction in seizure frequency which consistently showed some improvement. However, in future studies, it may be prudent to look also in other measures such as improvement in the motor strength or improvement in cognitive status.

Although not majority of the patients showed complete or partial response in the serial imaging done, it was shown that radiological change did not automatically translate to clinical change. In one of the studies, 33% of patients with only stable disease on imaging actually improved neurologically with significant decrease in seizure attacks [21]. Progression-free survival was similar in patients with CR/PR and in patients with stable disease [22]. What seems to affect the prognosis of the patient was the enhancement of the tumor in the imaging which may signify progressive disease both radiologically and clinically [20].

Conclusion

We conclude that Temozolomide showed consistently high overall survival and reduction in seizure frequency among patients diagnosed with LGG. Variable responses on objective radiologic response, quality of life and progression-free survival rates were noted. Future studies should look into the efficacy of Temozolomide as an adjunct treatment and as an initial treatment in LGG, with a comparison with a control group in order for more conclusions to be made. Also, MGMT and 1p/19q status should be taken into consideration when assessing chemotherapeutic response in patients.

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