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SUMMARY WITH CRITICAL APPRAISAL

Extended Dosing (12 Cycles) of Adjuvant Temozolomide in Adults with Newly Diagnosed High Grade Gliomas: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Context and Policy Issues

High-grade (Grade III or IV, classified by the World Health Organization [WHO]) gliomas are malignant, often rapidly progressive brain tumors. They grow faster and are more likely to recur even after treatment compared with low-grade gliomas, and therefore have poorer prognosis.[1,2] They can be categorized as anaplastic gliomas or glioblastoma based on their histopathologic and molecular features. Patients with high grade gliomas typically present neurologic signs and symptoms (e.g. headache, seizures, memory loss, motor weakness, visual symptoms, language deficit, cognitive and personality changes; and for large tumors, increased intracranial pressure is presented) that progress over days to weeks and vary according to the location and size of the tumor within the brain. While magnetic resonance imaging of the brain provides confirmatory evidence of a mass lesion, a tissue diagnosis is required to distinguish high-grade gliomas from other primary or metastatic brain tumors.[3] The incidence of glial tumors is estimated as 5.4 cases per 100,000 individuals in Europe and 5.3 per 100,000 in the United States (US).[4,5] Glioblastoma is the most frequent and most aggressive glial tumor in adults, representing 54% of all gliomas.[4] The incidence of high-grade gliomas in Canada was not identified in the literature.

For patients with a newly diagnosed high-grade glioma, the current standard of care includes maximal surgical resection (with preservation of neurologic function) followed by concurrent temozolomide (TMZ) and radiation therapy, and then maintenance TMZ (150 to 200 mg/m^2 for five days every 28 days for six cycles after radiotherapy).[6-9] TMZ is an oral alkylating agent that is used simultaneously with radiotherapy, as well as adjuvant chemotherapy after radiotherapy. In general, the prognosis of patients with high-grade gliomas is poor. In the modern era, post-operative radiation alone leads to median survivals of approximately one year, and the addition of the adjuvant TMZ therapy to radiation extends survival to 14 to 16 months.[10] Important prognostic factors affecting survival in this patient population are age (better if ≤ 50 years old), performance status (better if Karnofsky performance score [KPS] ≥ 70), histologic tumor type (anaplastic astrocytoma versus anaplastic oligodendroglioma) and grade, extended initial surgical resection, and certain molecular genetic alterations (isocitrate dehydrogenase [IDH]1-2, 1p/19q co-deletion and O_6-methylguanine-DNA methyltransferase [MGMT]).[3,11]

The clinical benefit of six cycles of adjuvant TMZ has been demonstrated in a number of clinical trials for newly diagnosed patients with high-grade gliomas after their surgery and radiotherapy, and is the current standard of care for this patient population.[4,9] Treatment with TMZ is associated with higher risk of hematologic toxicity, nausea, vomiting, fatigue and infections.[7,12] In practice, patients may receive prolonged adjuvant TMZ therapy with a duration of 12 or more cycles, given the hope of improving disease control in those without disease progression.[4] However, the benefits of extended TMZ therapy are uncertain. In recent years, clinical trials have been conducted to evaluate the benefits and harms associated to 12 cycles of TMZ therapy in patients with high-grade gliomas such as anaplastic glioma and glioblastoma. Improved survival was observed in patients received 12 cycles of TMZ following radiotherapy.[11,13,14] In one non-randomized controlled trial, TMZ therapy was discontinued due to toxicity in 8% of the study participants.[14] Treatment of high-grade gliomas can be expensive. An American study reported that the cost of

Temodar (brand name TMZ in the US) alone ranged from US$1,600 to US$4,600 per month, when the cost of surgical resection and radiotherapy were not considered.[15]

The purpose of this review is to identify the clinical evidence on 12 cycles of adjuvant TMZ for patients with newly diagnosed high-grade gliomas, and to examine the clinical and cost-effectiveness of this extended treatment regimen for these patients.

Research Questions

1. What is the clinical effectiveness of extended dosing (12 cycles) of adjuvant temozolomide in adult patients with newly diagnosed high grade gliomas?
2. What is the cost-effectiveness of extended dosing (12 cycles) of adjuvant temozolomide in adult patients with newly diagnosed high grade gliomas?
3. What are the evidence-based guidelines associated with the use of adjuvant temozolomide in adult patients with newly diagnosed high grade gliomas?

Key Findings

Evidence from two randomized controlled trials and one non-randomized controlled trial of adult patients with newly-diagnosed gliomas suggest that compared with the conventional 6-cycle adjuvant temozolomide therapy, the 12-cycle regimen was associated with improved survival outcomes, including overall survival and progression-free survival, although the between-group difference in overall survival was not statistically significant. The use of 12-cycle adjuvant temozolomide therapy was also related to higher risks of Grade 3-4 toxicities compared with the 6-cycle regimen, especially for hematological toxicities. However, the clinical effectiveness of extended dosing of adjuvant temozolomide relative to conventional 6-cycle regimen should be interpreted with caution, due to the compromised quality and the small sample size in some of the included trials.

Two evidence-based clinical practice guidelines developed in Spain recommend the use of 12-cycle adjuvant temozolomide therapy after surgery and radiotherapy, for newly-diagnosed glioblastoma in elderly patients (≥ 65 years) or anaplastic astrocytoma.

No relevant economic evaluations were identified from the literature to examine the cost-effectiveness of 12-cycle temozolomide therapy in the population of interest.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic studies, or guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and January 26, 2018.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with newly diagnosed high grade gliomas
Intervention	Extended dosing (12 cycles) of adjuvant temozolomide
Comparator	Q1: Current/regular dosing (6 cycles) of adjuvant temozolomide; no adjuvant temozolomide Q2: Current/regular dosing (6 cycles) of adjuvant temozolomide; no adjuvant temozolomide Q3: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., overall survival, progression-free survival, quality of life) and safety (patient harms, tolerability); Q2: Cost-effectiveness (e.g., cost per QALY increase) Q3: Guidelines
Study Designs	HTA/SRs/MAs, RCTs, non-randomized studies, economic evaluations, evidence-based guidelines

HTA = health technology assessment; MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review; QALY = quality-adjusted life year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Studies were excluded if the number of cycles of adjuvant TMZ was not specified. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included randomized and non-randomized studies were critically appraised using the Downs and Black checklist.[16] Guidelines were assessed with the AGREE II instrument.[17] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 321 citations were identified in the literature search. Following screening of titles and abstracts, 307 citations were excluded and 14 potentially relevant reports from the electronic search were retrieved for full-text review. No relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, nine publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two RCTs (Bhandari et al.[18] and van den Bent et al.[19]), one retrospective cohort study (Skardelly et al.[20]) and two clinical practice guidelines[11,12] were identified. Detailed study characteristics are provided by study type in Appendix 2.

Study Design

An open-label RCT[18] was conducted by Bhandari et al. to compare the clinical effectiveness of 12-cycle TMZ with conventional 6-cycle TMZ in post-operative patients with newly diagnosed glioblastoma (GB). Randomization was carried out with computer-generated random numbers. A sample size calculation was not performed due to the limited resources of the study.

The CATNON trial conducted by van den Bent et al. was a multi-country, multi-center, open-label phase 3 RCT that used a 2×2 factorial design.[19] Eligible patients were randomized 1:1:1:1 to four treatment arms: radiotherapy alone, radiotherapy and concurrent TMZ, radiotherapy with adjuvant TMZ (12 cycles), and radiotherapy and concurrent TMZ plus adjuvant TMZ (12 cycles). Randomization was carried out with a web-based patient registration and randomization system developed by the European Organization for Research and Treatment of Cancer (EORTC). Patients were stratified by institution, performance status score (> 0 vs. 0), 1p loss of heterozygosity (yes vs. no), presence of liogodendroglial elements on microscopy (yes vs. no), and MGMT promoter methylation status. The sample size (748 patients, 523 deaths) was calculated to provide 83% power to detect a risk reduction of 0.8 for patients receiving radiotherapy with concurrent and adjuvant TMZ, compared with those receiving radiotherapy alone, at a significance level of 5%. The study is still ongoing and the estimated completion date is January 2024.[21] A planned interim analysis was conducted when 219 (41%) deaths occurred. At that time, 745 (99%) of the planned 748 patients had been enrolled. Results of the interim analysis of CATNON were reported in the published article.[19]

A retrospective cohort study was conducted in a single center in Germany to examine the impact of prolonged TMZ maintenance therapy beyond six cycles in newly diagnosed GB.[20] It is unclear whether a sample size calculation was performed for this study. Baseline patient characteristics such as age, extent of resection, MGMT status and KPS score were controlled for in the data analysis.

Two evidence-based guidelines[11,12] providing guidance on treatment of high-grade gliomas (anaplastic gliomas and glioblastoma) were identified. Information regarding guideline development and methodology was not described in detail. The guideline for glioblastoma[12] was developed with the consensus of 10 physicians with different specialties. During the development of guideline for anaplastic gliomas,[11] a systematic review of the literature was conducted by an expert multidisciplinary panel to identify evidence on diagnoses, treatment and follow-up of anaplastic gliomas. In both guidelines, the US Preventive Services Task Force (USPSTF) Grading System was adopted to assess the levels of evidence, and grade the guideline recommendations accordingly. The level of evidence was graded from I to V with I being high quality (evidence from at least one well-conducted RCT or meta-analysis of well-conducted RCTs without heterogeneity) and V being low quality (evidence from uncontrolled studies, case reports, expert opinion). Grade of recommendations was classified from A to E with A being "strongly recommended" and E being "never recommended".

Country of Origin

The RCT by Bhandari et al. was conducted in India.[18] The CATNON trail was a multi-country, multi-center study that was conducted in Europe, Australia and Canada.[19] The cohort study was conducted in Germany.[20]

Both guidelines were jointly developed by the Spanish Society of Medical Oncology (SEOM) and the Spanish Group for Research on Neuro-Oncology (GEINO) in 2017.[11,12]

Patient Population

In the RCT by Bhandari et al.,[18] postoperative adult patients with confirmed histopathology of GB were recruited. They were required to have a KPS ≥ 70. Patients with recurrent or metastatic disease were excluded from the study.

In the CATNON trial, adult patients with newly diagnosed anaplastic glioma without 1p/19q co-deletion and WHO performance status scores of 0-2 were enrolled.[19]

In the cohort study,[20] adult patients with newly diagnosed GB who received standard radiotherapy with concomitant and maintenance TMZ were identified via an electronic administrative database search. All these patients underwent surgery in this single center from January 2006 to December 2014. Patients who discontinued concomitant radiochemotherapy for any reason were excluded from the study.

Guideline Intended Users and Target Population

Intended users of both of the included SEOM guidelines were healthcare professionals of all disciplines involved in the diagnosis and care of patients with GB and anaplastic gliomas.[11,12] The target populations for the guidelines were adult patients with GB,[12] and anaplastic gliomas[11] (including anaplastic astrocytomas (AA) and anaplastic oligodendroglioma [AOD]).

Interventions and Comparators

In the RCT by Bandari et al.,[18] eligible participants in both treatment groups received maximum safe surgical resection, sub-total excision, or decompression only, and received a similar regimen of concurrent chemoradiotherapy, followed by 6- or 12-cycle adjuvant TMZ, at a dose of 150 mg/m^2 for the first cycle and 200 mg/m^2 for the subsequent cycles, when it was tolerable. Twenty patients were randomly assigned to each treatment group.

In the CATNON trial, eligible patients were randomized 1:1:1:1 to receive: radiotherapy with (n=185) or without adjuvant TMZ (n=187), or radiotherapy and concurrent TMZ with (n=188) or without adjuvant TMZ (n=185). Therefore, the number of patients received the adjuvant TMZ therapy was 373, and the number of patients without adjuvant TMZ was 372. The concurrent TMZ was given daily at a dose of 75 mg/m^2 for a maximum of seven weeks. Adjuvant TMZ started four weeks after completion of radiotherapy for a maximum of 12 4-week cycles, at a dose of 150-200 mg/m^2/day given on days 1-5 in the first cycle and 200 mg/m^2 on days 1-5 of the following cycles, if no or minor toxicity was observed during the first cycle.

In the cohort study, the number of cycles of TMZ maintenance therapy was determined by the treating physicians.[20] Study participants were divided into three groups according to the received TMZ therapy: 0-5 cycles of TMZ, 6 cycles of TMZ and > 6 cycles of TMZ. The dose of TMZ was not specified in this study. In the study, the median number of completed cycles of TMZ was 1, 6 and 12 cycles for the aforementioned treatment groups.

The two guidelines relevant to this report considered surgery, radiotherapy and systematic treatment including TMZ for the treatment of adult patients with newly diagnosed or recurrent GB, AA or AOD, respectively.[11,12]

Outcomes

The Bhandari trial evaluated overall survival, progression-free survival and harms.[18] The primary outcome in the CATNON trial[19] was overall survival adjusted by all stratification factors except institution. Progression-free survival adjusted for stratification factors was also assessed. The primary analysis in the CATNON trial was performed in the intention-to-treat population, which was defined as all patients randomly assigned to a treatment group. Findings on survival probability were presented with 95% or 99% confidence intervals (CIs) to describe the random variability in the data: the 95% CIs were presented in the univariate analyses of the overall and progression-free survival using the Kaplan-Meier technique, and the 99% CIs were presented in the analysis of overall survival using a Cox proportional hazards model to adjust for stratification factors.

In both RCTs, overall survival was calculated from the date of randomization to the date of death from any cause, and progression-free survival was defined as the time from randomization to the date of first progression or death, whichever came first. Toxicity during the treatment was evaluated using the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0.

The cohort study examined the overall survival and progression-free survival of the extended cycle of TMZ in the study population.[20] These outcomes were defined as the interval between initial surgery and death of the patient or the first radiologically documented disease progression, respectively. Subgroup analyses on overall survival were performed for the covariates of age (≤ 50 years vs. > 50 years), performance status score (< 70 vs. ≥ 70), MGMT gene promoter, extent of resection (gross total vs. subtotal and biopsy), and gender.

The main relevant outcomes considered in both SEOM guidelines were overall survival, progression-free survival, and adverse events of the treatment.[11,12]

Summary of Critical Appraisal

A detailed summary of the critical appraisal of each included study is provided in Appendix 3.

Randomized controlled trials

Both RCTs[18,19] clearly reported the methods, including descriptions of the study objectives, patient inclusion and exclusion criteria, interventions, comparators, and outcomes. The Bhandari RCT included a small group (N=40) of patients with GB, and a sample size calculation was not performed due to limited resources. It is therefore unclear whether it had sufficient power to detect a clinically important effect. The enrolled patients are considered representative of those seen in the clinical practice; however the baseline patient characteristics were somewhat imbalanced between the two treatment arms (i.e. patients in the extended cycle arm were younger, fewer females, had lower KPS score, relatively larger tumor size and longer duration since symptom presentation). There were no patients who withdrew from the study. This was an open-label study, but the study design is unlikely to have a significant impact on the survival outcomes, which were objective measurements. It is unclear whether the supporting care might be different

between treatment groups when patients and healthcare providers were aware of the treatment regimen. The Bhandari RCT was of moderate quality given its small sample size, inadequate data reporting, and the associated challenges in data interpretation. The authors declared no conflict of interest.

The CATNON trial was well designed and of high quality.[19] This was an open-label study. Only findings from the interim analysis were available in the published article. A total of 745 patients (99% of the required sample size) were included in the interim analysis. Baseline characteristics, such as patient demographics, diagnoses, disease characteristics and details of previous treatment, were comparable across treatment arms. Patient disposition was reported and the primary analysis was conducted in the intention-to-treat population. Among the patients receiving 12 cycles adjuvant TMZ therapy, 106 (28.4%) discontinued TMZ. It is unclear how these data were accounted for in the analysis. Grade 3 or 4 toxicities were reported for patients receiving concurrent and adjuvant TMZ; however, there were no safety data available specifically for those receiving the adjuvant TMZ. The study was sponsored by industry and non-industry funding.

Non-randomized study

For the non-RCT, quality of this study was compromised due to the nature of the study design, in that patients were not randomly allocated to the investigated treatment modalities. Treatment regimen was chosen by the physicians. Selection bias is likely to be introduced in this manner. Imbalanced baseline patient characteristics, such as age and extent of resection between the 6 cycles TMZ group and > 6 cycles TMZ group were observed across the treatment groups. Multivariate Cox regressions was used to control for the known confounders (i.e. age, performance status and extent of resection), and adjusted survival rates were reported in the study. The impact of study design on the clinical outcomes may be lessened by this approach. Another major limitation was that the study may not have sufficient power to detect a true between-group difference due to the small sample size (N=107).

Evidence-based guidelines

In the two SEOM guidelines, the overall objective, the scope and rationale of the guidelines were specifically described.[11,12] The guideline for GB[12] indicated that physicians from different specialties (not specified) with dedication to neuro-oncology were involved in the guideline development process, while the guideline for AA and AOD[11] did not specify which professional groups were involved. The guideline for GB stated that its aim was to provide evidence-based recommendations for clinical practice to medical professionals involved in the diagnosis and care of patients with GB, without providing more details with respect to the guideline development process and methods.[12] A systematic literature search strategy was employed to identify relevant evidence according to the authors of the guideline for AA and AOD.[11] For both guidelines, a grade for the whole body of evidence supporting each recommendation was determined, and the working group then reviewed the strength of the evidence and generated recommendations accordingly. In addition to the recommendations, the working group also provided a grade to indicate the strength of the recommendation. However, the methods for formulating the recommendations are not described in details. Specific recommendations were easily identifiable, and presented considerations for special populations (i.e. patients > 65 years of age) and different options for management of the applicable condition. Authors of these guidelines declared that they had no conflict of interest. It is noteworthy that in the guideline of GB,[12] even though 12 cycles of adjuvant TMZ was recommended for the target population, the evidence

supporting this recommendation actually derived from one single RCT, where the median number of cycles of adjuvant TMZ was five. Each author approved the final version of the guidelines, but it is unclear whether the guidelines were externally reviewed.

Additional details regarding study strengths and limitations are provided in Appendix 3.

Summary of Findings

Five publications regarding the clinical effectiveness and harms of or guidelines for extended dosing of adjuvant TMZ in adult patients with newly diagnosed high-grade gliomas met the inclusion criteria for this review. Details of the main study findings and authors' conclusions are presented in Appendix 4.

What is the clinical effectiveness of extended dosing (12 cycles) of adjuvant temozolomide in adult patients with newly diagnosed high grade gliomas?

Overall survival

In the Bhandari RCT, the median overall survival was 23.8 months in the 12-cycle TMZ group, compared to 15.4 months in the 6-cycle TMZ group (statistical significance not reported).[18] The 2-year overall survival rates were 35.5% in the 12-cycle TMZ group versus 12.9% in the 6-cycle TMZ group, *P* = 0.044.

In the CATNON trial, 745 (99%) of the planned 748 patients had been enrolled at the time of interim analysis.[19] The hazard ratio (HR) for overall survival with use of 12 cycles of adjuvant TMZ was 0.65 (99% CIs: 0.45 to 0.93), indicating a 35% reduction in the risk of death compared with non-adjuvant TMZ treatment groups. The 5-year survival rate was 55.9% (95% CI: 47.2 to 63.8) with adjuvant TMZ and 44.1% (95% CI: 36.3 to 51.6) without adjuvant TMZ, respectively.

In the cohort study, the median overall survival was 25.2 months (95% CI: 17.7 to 55.5) in the 6 cycle TMZ group and 28.6 months (95% CI: 24.4, open) in the > 6 cycles TMZ group.[20] However, results of the multivariate Cox regression indicated no statistically significant difference in overall survival between patients receiving > 6 cycles TMZ and those who received exactly 6 cycles TMZ (relative risk [RR] 0.77; 95% CI: 0.39, 1.55; *P* = 0.46).

Progression-free survival

In the Bhandari RCT, the median progression-free survival was 18.7 months in the 12-cycle TMZ group, compared to 16.4 months in the 6-cycle TMZ group (statistical significance was not reported).[18] The 2-year progression-free survival rates were 35.5% in the 12-cycle TMZ group versus 12.9% in the 6-cycle TMZ group, *P* = 0.069.

In the CATNON trial, at the time of interim analysis, the HR for progression-free survival with 12 cycles of adjuvant TMZ was 0.62 (95% CI: 50 to 0.76), indicating a 38% reduction in the risk of disease progression and/or death compared with non-adjuvant TMZ treatment groups.[19]

In the cohort study, the median progression-free survival was 13.7 months (95% CI: 10.6 to 17.5) in the 6 cycles TMZ group and 20.9 months (95% CI: 15.2 to 43.5) in the > 6 cycle TMZ group.[20] Results of the multivariate Cox regression indicated a statistically significant difference in disease progression between patients receiving > 6 cycles TMZ and those who received exactly 6 cycles TMZ (RR 0.52; 95% CI: 0.28 to 0.94; *P* = 0.03).

Adverse events

In the Bhandari RCT,[18] 5% and 15% of patients in the 6-cycle TMZ group and 12-cycle TMZ group had ≥ Grade 3 hematological toxicity, respectively: one case of Grade 3 thrombocytopenia was reported in the 6-cycle group, while in the 12-cycle group, one Grade 3 thrombocytopenia, one Grade 3 neutropenia and one Grade 4 thrombocytopenia were reported.

In the CATNON trial, Grade 3-4 adverse events were reported in 8-12% of 549 patients assigned TMZ, including concurrent and adjuvant TMZ therapy, with thrombocytopenia being the most frequently reported event (7-9%).[19] Among patients receiving adjuvant TMZ, 106 (28.4%) discontinued TMZ due to: progressive disease or death (56 patients), toxicity (30), patient refusal (9) and other reasons (11). There were no safety data specifically reported for patients receiving adjuvant TMZ.

What is the cost-effectiveness of extended dosing (12 cycles) of adjuvant temozolomide in adult patients with newly diagnosed high grade gliomas?

No economic evaluations were identified for this review.

What are the evidence-based guidelines associated with the use of adjuvant temozolomide in adult patients with newly diagnosed high grade gliomas?

Based on the findings from an open-label RCT (Level I evidence) of elderly patients, the SEOM guideline for GB recommends that radiotherapy plus concurrent TMZ, followed by 12 cycles adjuvant TMZ for newly diagnosed elderly patients (> 65 year old).[12] The strength of the recommendation was graded as A, indicating "strong evidence for efficacy with a substantial clinical benefit, strongly recommended". It is noteworthy that in the treatment arm of radiotherapy plus TMZ of this RCT, even though patients were allowed to receive up to 12 cycles of adjuvant TMZ, the median number of delivered cycles was five and the range of number of delivered cycles was not reported.

The SEOM guideline for anaplastic gliomas recommends that post-operative radiotherapy and TMZ treatment for 12 cycles are used for patients with newly-diagnosed AA, according to the interim results of the CATNON trial (Level I evidence; Grade B recommendation, indicating strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended).[11]

Limitations

The evidence regarding the clinical effectiveness of 12-cycle adjuvant TMZ for adult patients with high-grade gliomas was limited to two RCTs and one cohort study. One RCT[18] and the cohort study[20] compared the 12-cycle regimen with the conventional 6-cycle regimen; however, both studies had a small sample size, and patient's baseline characteristics were imbalanced between treatment groups. There may not have sufficient power to detect statistically significant between-group differences if there were any. The results should be interpreted with caution. The second RCT (CATNON)[19] was a well-designed, multi-center, phase 3 study. However, only the results of interim analysis were available at the time of this review. The 12-cycle TMZ therapy was compared with no adjuvant therapy; therefore it did not provide direct evidence to evaluate the clinical benefits and harms of 12-cycle TMZ regimen relative to the standard 6-cycle TMZ regimen.

In addition, there were no relevant economic evaluations identified to address the cost-effectiveness of 12-cycle adjuvant TMZ therapy compared with the standard 6-cycle TMZ

therapy for the target population. The quality of the identified practice guidelines was compromised due to insufficient information provided regarding the methods of recommendation formulation. For one guideline, the link between generated recommendation and the supporting evidence is questionable.[12]

Conclusions and Implications for Decision or Policy Making

In total, two RCTs and one cohort study have been examined in the current report. All patients had newly diagnosed high-grade gliomas (glioblastoma and anaplastic astrocytoma). Sample size in the studies ranged from 40 to 745 adults. The treatment effect of 12-cycle adjuvant TMZ therapy was compared with a conventional 6-cycle regimen in two studies, following surgery and radiotherapy. Evidence from these studies suggests that compared with the standard 6-cycle TMZ therapy, prolonged TMZ therapy was associated with improved survival outcomes, including overall survival and progression-free survival, but higher risks of Grade 3-4 hematological toxicity. Results from the non-randomized trial suggested that the between-group difference in overall survival may not be statistically significant. The clinical effectiveness of 12-cycle adjuvant TMZ therapy relative to the standard 6-cycle regimen for the target population should be interpreted with caution, due to the compromised quality and the small sample size in some of the included trials.

Two evidence-based clinical practice guidelines developed in Spain recommend the use of 12-cycle adjuvant TMZ therapy after surgery and radiotherapy, for newly-diagnosed glioblastoma in elderly patients (≥ 65 years) or anaplastic astrocytoma.

There were no economic evaluations identified to assess the cost-effectiveness of 12-cycle adjuvant TMZ in patients with high-grade gliomas.

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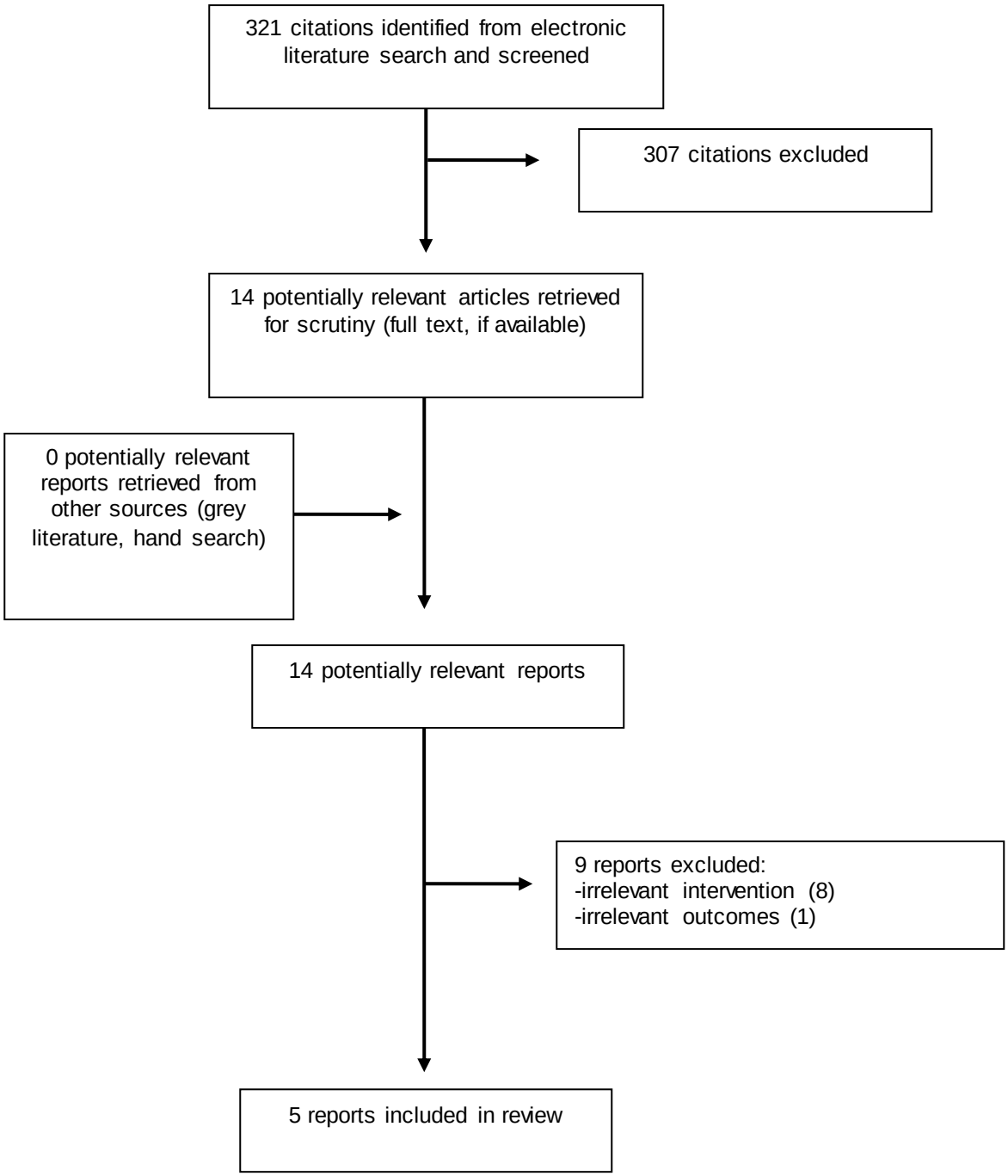
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First author, Publication year, Study name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Bhandari 2017[18]	Open-label RCT	Adults (18-65 years old) with newly diagnosed, histologically confirmed GB. WHO performance status scores of 0-2. Adequate hematological, renal, and liver function.	12-cycle adjuvant TMZ (n=20)	6-cycle adjuvant TMZ (n=20)	OS, PFS, safety
Van den Bent 2017[19], the CATNON Trial	Open-label RCT, phase 3, multi-country	Adults (≥ 18 years old) with newly diagnosed anaplastic glioma without 1p/19q co-deletion. The KPS ≥ 70. Adequate hematological, renal and liver function. Patients with recurrent or metastatic disease were excluded.	Radiotherapy + 12-cycle adjuvant TMZ (n=185) Radiotherapy + concurrent TMZ + 12-cycle adjuvant TMZ (n=188)	Radiotherapy alone (n=187) Radiotherapy + concurrent TMZ (n=185)	OS, PFS, safety
Skardelly, 2017[20]	Retrospective cohort study, single-center	Adults ((≥ 18 years old) with newly diagnosed GB. Exclusion: patients who discontinued concomitant radiochemotherapy for any reason.	TMZ maintenance therapy = 6 cycles (n=32)	TMZ maintenance therapy ≤ 5 cycles (n=32) TMZ maintenance therapy > 6 cycles (n=43)	OS, PFS

GB = glioblastoma; KPS = Karnofsky Performance Score; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; TMZ = temozolomide; WHO = the World Health Organization.

Table A2: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/target population	Intervention and Practice considered	Major outcomes considered	Evidence, collection, selection and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Guidelines for GB, SEOM, 2017[12]						
Intended users: Healthcare professionals of all disciplines involved in the diagnosis and care of patients with GB Target population: adult patients with newly diagnosed or recurrent GB	Diagnosis, treatment and follow-up for GB	Overall survival, progression-free survival, safety	Not specified	USPSTF grading system	10 physicians with different specialties were involved in the working group; evidence was identified and appraised, and recommendations were formulated according to the levels of evidence. Other details not provided.	Not specified.
Guidelines for AA and AOD, SEOM, 2017[11]						
Intended users: Healthcare professionals of all disciplines involved in the diagnosis and care of patients with anaplastic gliomas Target population: population: adult patients with newly diagnosed or recurrent AA or AOD	Diagnosis, treatment and follow-up for AA and AOD	Overall survival, progression-free survival, safety	Systematic review, no details provided for the searched databases and time frame.	USPSTF grading system	An expert multidisciplinary panel was formed to conduct a systematic review of the literature; level of evidence and grade of recommendation were assessed. Other details not provided.	Each author approved the final version of the guideline.

AA = anaplastic astrocytoma; AOD = anaplastic oligodendroglioma; GB = glioblastoma; USPSTF = the US Preventive Services Task Force

Appendix 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Randomized and Non-Randomized Trials using Downs and Black Checklist[16]

Strengths	Limitations
Bhandari 2017[18]	
• The study objective was clearly described • Patient inclusion and exclusion criteria were provided • Interventions, comparators, and main outcomes were clearly described • Methods of randomization were appropriate • Actual probability values reported • Appropriate statistical tests were used to assess the main outcomes; • No patients dropped out; all patients were included in analysis • Main outcome measures were clearly described • Patients in both treatment groups were recruited from the same facility, over the same period of time • Conflict of interest was declared	• Patients were not blinded to the intervention they received • Small sample size; sample size calculation was not performed • Baseline patient characteristics were imbalanced between treatment groups • Actual probability values (i.e. p values and 95% CIs) were not always reported • Adverse events associated with intervention were briefly reported • Other important clinical outcomes such as health-related quality of life were not reported
Van den Bent 2017[19]	
• The study objective was clearly described • Patient inclusion and exclusion criteria were provided • Interventions, comparators, and main outcomes were clearly described • Methods of randomization were appropriate • Adverse events associated with intervention were considered • Actual probability values were reported • Appropriate statistical tests were used to assess the main outcomes; analysis was based on intention-to-treat population • Main outcome measures were clearly described • Sample size calculation was performed • Conflict of interest and funding sources were reported	• Patients were not blinded to the intervention they received • 12 cycles TMZ therapy was compared with no adjuvant TMZ therapy, instead of 6 cycles TMZ • 30 patients (8%) treated with 12 cycles adjuvant TMZ did not complete the study • Only results of interim analysis were available • Other important clinical outcomes such as health-related quality of life were not reported
Skardelly 2017[20]	
• The study objective was clearly described • Patient inclusion and exclusion criteria were provided • Interventions, comparators, and main outcomes were described in the methods section, although the dose of TMZ was not provided • Appropriate statistical tests were used to assess the main outcomes • Main outcome measures were clearly described • Conflict of interest and funding sources were reported	• Adverse events associated with intervention were not assessed • Actual probability values were not always reported • There was no sample size calculation • Study participants were recruited from the same facility, over an 8-year period of time

Table A4: Strengths and Limitations of Guidelines using AGREE II[17]

Item	SEOM Guideline for GB[12]	SEOM Guideline for AA and AOD[11]
Domain1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	√	√
2. The health question(s) covered by the guideline is (are) specifically described.	√	√
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	√	√
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	unclear	unclear
5. The views and preferences of the target population (patients, public, etc.) have been sought.	unclear	unclear
6. The target users of the guideline are clearly defined.	√	√
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	unclear	√
8. The criteria for selecting the evidence are clearly described.	X	X
9. The strengths and limitations of the body of evidence are clearly described.	X	X
10. The methods for formulating the recommendations are clearly described.	√	√
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	√	√
12. There is an explicit link between the recommendations and the supporting evidence.	X	√
13. The guideline has been externally reviewed by experts prior to its publication.	X	X
14. A procedure for updating the guideline is provided.	X	X
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	√	√
16. The different options for management of the condition or health issue are clearly presented.	√	√
17. Key recommendations are easily identifiable.	√	√
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	X	X
19. The guideline provides advice and/or tools on how the	√	√

Item	SEOM Guideline for GB[12]	SEOM Guideline for AA and AOD[11]
recommendations can be put into practice.		
20. The potential resource implications of applying the recommendations have been considered.	X	X
21. The guideline presents monitoring and/or auditing criteria.	X	X
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	√	√
23. Competing interests of guideline development group members have been recorded and addressed.	X	X

AA = anaplastic astrocytoma; AOD = anaplastic oligodendroglioma; GB = glioblastoma;

Appendix 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Bhandari et al., 2017 (RCT)[18]	
Overall survival: ○ Median survival: 23.8 months for 12 cycles TMZ vs. 15.4 months for 6 cycles TMZ ○ 2-year overall survival: 35.5% for 12 cycles TMZ vs. 12.9% for 6 cycles TMZ, p=0.044. Progression-free survival: ○ Median progression-free survival: 16.8 months for 12 cycles TMZ vs. 12.8 months for 6 cycles TMZ. ○ 2-year progression-free survival: 18.7% for 12 cycles TMZ vs. 16.4% for 6 cycles TMZ, p=0.069.	12-cycle of adjuvant TMZ therapy "*is well-tolerated and leads to a significant increase in PFS as well as OS in newly diagnosed patients of GBM*". – Bhandari 2017[18], pg.4
The CATNON Trial, 2017 (RCT)[19]	
Overall survival: ○ HR for use of adjuvant 12 cycles TMZ: 0.65 (99-145% CI: 0.45, 0.93), p=0.0014. ○ Median survival: not reached for adjuvant 12 cycles TMZ vs. 41.1 months (95% CI: 36.6, 60.7) for no adjuvant TMZ. ○ 5-year overall survival: 55.9% (95% CI: 47.2, 63.8) for adjuvant 12 cycles TMZ vs. 44.1% (95% CI: 36.3, 51.6) for no adjuvant TMZ. Progression-free survival: ○ HR for use of adjuvant 12 cycles TMZ: 0.62 (95% CI: 0.50, 0.76) ○ Median progression-free survival: 42.8 months (95% CI: 28.6, 60.6) for adjuvant 12 cycles TMZ vs. 19.0 months (95% CI: 14.4, 24.6) for no adjuvant TMZ. ○ 5-year progression-free survival: 43.1% (95% CI: 35.0, 50.9) for adjuvant 12 cycles TMZ vs. 24.3% (95% CI: 17.7, 31.6) for no adjuvant TMZ.	Adjuvant TMZ "*was associated with a significant survival benefit in patients with newly diagnosed non-co-deleted anaplastic glioma*". – van den Bent 2017[19], pg.3
Skardelly et al., 2017 (cohort study)[20]	
Overall survival: ○ Adjusted RR for > 6 cycles TMZ compared to 6 cycles TMZ: 0.77; 95% CI: 0.39, 1.55; p = 0.46. ○ Median survival: 28.6 months (95% CI: 24.4, open) for > 6 cycles TMZ vs. 25.2 months (95% CI: 17.7, 55.5) for 6 cycles TMZ. ○ 2-year overall survival: 68% for > 6 cycles TMZ vs. 51% for 6 cycles TMZ. Progression-free survival: ○ Adjusted RR for > 6 cycles TMZ compared to 6 cycles TMZ: 0.52; 95% CI: 0.28, 0.94; p = 0.03. ○ Median progression-free survival: 20.9 months (95% CI: 15.2, 43.5) for > 6 cycles TMZ vs. 13.7 months	"*Multivariate Cox regression and adjusted survival curve analysis did not suggest a benefit in hazard rates for prolonged TMZ maintenance therapy on OS (p=0.46) but did on PFS (p=0.03)*" – Skardelly 2017[20], pg. 574. "*Our data do not support a general extension of TMZ maintenance therapy beyond six cycles*" – Skardelly 2017[20], pg.575

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
(95% CI: 10.6, 17.5) for 6 cycles TMZ. ○ 2-year progression-free survival: 48% for > 6 cycles TMZ vs. 26% for 6 cycles TMZ.	

CI = confidence interval; GBM = glioblastoma multiforme; HR = hazard ratio; RR = relative risk; TMZ = temozolomide.

Table A6: Summary of Recommendations in Included Guidelines

Findings and Recommendations	Grade/Strength of Recommendation
SEOM Guideline for GB, 2017[12]	
Post-operative radiotherapy (40 Gy in 15 sessions) plus concurrent TMZ, and followed by adjuvant TMZ for 12 cycles are recommended for newly-diagnosed elderly patients with GB (≥ 65 years).	Grade A recommendation, strongly recommended
SEOM Guideline for AA and AOD, 2017[11]	
Post-operative radiotherapy and TMZ treatment for 12 cycles are recommended for newly-diagnosed patients with AA.	Grade A recommendation, strongly recommended

AA = anaplastic astrocytoma; AOD = anaplastic oligodendroglioma; GB = glioblastoma; TMZ = temozolomide.

Appendix 5: Additional References of Potential Interest

Systematic Reviews with unspecified number of cycles of temozolomide

Xu W, Li T, Gao L, Zheng J, Shao A, Zhang J. Efficacy and safety of long-term therapy for high-grade glioma with temozolomide: A meta-analysis. Oncotarget [Internet]. 2017 Aug 1 [cited 2018 Jan 30];8(31):51758-65. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5584285

Primary Studies with prolonged, but not 12 cycles of temozolomide

Refae A, Ezzat A, Salem DA, Mahrous M. Protracted adjuvant temozolomide in glioblastoma multiforme. Journal of Cancer Therapy. 2015; 6(8):748-758.

Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med [Internet]. 2017 Mar 16 [cited 2018 Feb 12];376(11):1027-37. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1611977