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Quality of life in glioblastoma after the introduction of temozolomide: a systematic review

Qualidade de vida no glioblastoma após a introdução da temozolomida: uma revisão sistemática

Calidad de vida en glioblastoma después de la introducción de temozolomida: una revisión sistemática

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Abstract
Introduction: Gliomas are primary tumors of the central nervous system with an aggressive pattern of progression with a poor prognosis in terms of survival and quality of life. The current standard treatment consists of surgery with maximum excision associated with radiotherapy and chemotherapy, based mostly on the use of temozolomide. Since its introduction, the quality of life of patients undergoing this therapy has not been widely targeted and evaluated. Objective: To verify the quality of life of patients with glioblastoma after the introduction of temozolomide in the therapeutic protocols. Methods: A systematic literature review guided by the PICO and PRISMA protocol was conducted; PubMed, Medline and Lilacs databases were consulted. Results: Initially, 77 studies were found, after selection criteria, 35 articles were analyzed. No statistically significant change was found in overall quality of life in studies that analyzed temozolomide therapy versus different control therapies. Conclusion: The association of temozolomide with surgery and radiotherapy proved to be neutral, with no significant negative or positive impacts on the quality of life of patients with glioblastoma.
Keywords: Quality of life; Glioblastoma; Temozolomide.

Resumo
Introdução: Gliomas são tumores primários do sistema nervoso central com padrão agressivo de progressão com prognóstico ruim quanto a sobrevida e qualidade de vida. O tratamento padrão atual consiste em cirurgia com excisão máxima associado a radioterapia e quimioterapia, pautada majoritariamente pelo uso da temozolomida. Desde sua introdução, a qualidade de vida dos pacientes submetidos a essa terapia não foi amplamente objetivada e avaliada. Objetivo: Verificar a qualidade de vida dos pacientes portadores de glioblastoma após a introdução da temozolomida nos protocolos terapêuticos. Métodos: Foi conduzida revisão sistemática da literatura guiada pelo protocolo PICO e PRISMA; consultadas as bases de dados do PubMed, Medline e Lilacs. Resultados: Inicialmente encontrados 77 estudos, após critérios de seleção foram analisados 35 artigos. Não foi encontrada alteração estatisticamente significativa na qualidade de vida global nos estudos que analisaram a terapia com temozolomida frente às diferentes terapias controle. Conclusão: A associação da temozolomida à cirurgia e radioterapia se mostrou neutra, sem impactos negativos ou positivos consideráveis na qualidade de vida dos pacientes portadores de glioblastoma.
Palavras-chave: Qualidade de vida; Glioblastoma; Temozolomida.

Resumen
Introducción: Los gliomas son tumores primarios del sistema nervioso central con un patrón agresivo de progresión con mal pronóstico en términos de supervivencia y calidad de vida. El tratamiento estándar actual consiste en cirugía con escisión máxima asociada a radioterapia y quimioterapia, en su mayoría basada en el uso de temozolomida. Desde su introducción, la calidad de vida de los pacientes que se someten a esta terapia no ha sido objeto de una evaluación amplia. Objetivo: verificar la calidad de vida de los pacientes con glioblastoma después de la introducción de temozolomida en los protocolos terapéuticos. Métodos: Se realizó una revisión sistemática de la literatura guiada por

el protocolo PICO y PRISMA; Se consultaron las bases de datos PubMed, Medline y Lilacs. Resultados: Inicialmente se encontraron 77 estudios, luego de criterios de selección se analizaron 35 artículos. No se encontraron cambios estadísticamente significativos en la calidad de vida general en los estudios que analizaron la terapia con temozolomida versus diferentes terapias de control. Conclusión: La asociación de temozolomida con cirugía y radioterapia resultó ser neutra, sin impactos negativos o positivos significativos en la calidad de vida de los pacientes con glioblastoma.
Palabras clave: Calidad de vida; Glioblastoma; Temozolomida.

1. Introduction

Gliomas are primary tumors of the central nervous system, originating in aggregates of stem and progenitor cells of neural tissue, especially the neuroglia that are located in the subventricular zone, subcortical white matter and in the dentate gyrus of the hippocampus. Clinically, they appear more frequently in the frontal and temporal lobes, rarely affecting the brainstem and spinal cord (Wirsching et al., 2016).

There is a higher incidence in men, with a mean age of diagnosis at 65 years, causing high morbidity and mortality. Statistics vary according to geographic location and exposure to risk factors – most notably ionizing radiation and family history (Sim et al., 2021; Braun & Ahluwalia, 2017). The clinical presentation depends on the location, mass effect and tissue necrosis, most often asymptomatic in early stages, but commonly complicating with headache, epilepsy and focal neurological symptoms, especially aphasia (Wirsching et al., 2016).

Current treatment is based on the association of surgery with maximum resection of the lesion, radiotherapy and adjuvant chemotherapy, especially with temozolomide (Sim et al., 2021). Some factors are cited as determinants for the choice of therapy: age - patients younger than 65 years benefit more; systemic involvement index classically assessed by the Karnofsky performance scale (KPS); presence of comorbidities and the MGMT marker – drug resistance indicator (Braun & Ahluwalia, 2017; Domenech et al., 2021).

The preferred surgical modality is maximal resection of the lesion, guided by image such as ultrasound or magnetic resonance imaging, better tolerated by younger patients – less than 65 years old – and with a higher Karnofsky prognostic index (KPS), mainly due to the size of the surgery (Braun & Ahluwalia, 2017). It confers a variable survival gain, without major changes in quality of life (Wirsching et al., 2016), due to the functional impairment already established by the loss of healthy brain tissue at the time of diagnosis and approach, however, it can have complications inherent to any surgical act - site infection surgery, anesthetic complications and prolonged periods of hospital stay (Wirsching et al., 2016).

Radiotherapy is classically performed after the surgical approach, using standard protocols or with hypofractionated doses – the latter with a longer time interval between the doses of radiation applied and not inferior to the former in terms of survival results and quality of life when analyzed. by intention to treat (Braun & Ahluwalia, 2017), although in samples over 65 years of age no significant difference was observed in quality of life, survival and changes in performance scores when comparing classic regimens and hypofractionated doses (Wirsching et al., 2016; Domenech et al., 2021).

Temozolomide is an orally used alkylating agent that acts by damaging the genetic material by adding a methyl radical to the purine and pyrimidine groups. Since its introduction, it has shown an increase in survival compared to the current therapy – association of surgery and radiotherapy, from three months to two years in some series. The drug's action is limited by MGMT, a genetic promoter that repairs nitrogenous bases; when this marker is methylated , MGMT- methylated variant , the effects of temozolomide are greater and the prognosis is better (Braun & Ahluwalia, 2017; Karachi et al., 2018).

Generally well tolerated, it does not usually cause major adverse effects. It can lead to fatigue, nausea, vomiting and constipation, although these are partly due to the neoplasm and radiotherapy itself. More worrying are myelosuppression and immunosuppression, which can be complicated by opportunistic infections; however, such effects gained prominence with increased immune response even with lymphopenia , even more when associated with immunobiologicals in treatment

strategies that involve immunotherapy , since it has been observed that in lymphopenia there is greater antitumor activity secondary to greater antigen-specific immune response (Karachi, Dastmalchi, Mitchel & Rahman, 2018; Davis & Mulligan Stoiber, 2011; Stahl, *et al.*, 2020).

In addition to the low five-year survival rate, the quality of the time remaining for patients is low, not restricted to the patients themselves, but affecting family members and the entire environment. Although most studies focus on prolonging life, few focus on quality of life, leading to an ethical dilemma about dysthanasia (Davis & Mulligan Stoiber, 2011; Stahl, *et al.*, 2020; Baba & Adali, 2021).

Baba and Adali (2021) cite a considerable reduction in orientation, attention, calculation speed and language fluency with the use of temozolomide and radiotherapy. However, there is heterogeneity and lack of specific scales to assess the quality of life in glioblastoma, making an analysis with greater methodological rigor difficult (Domenech, Hernandez & Balana, 2021).

The European Organization for the Treatment of Cancer (EORTC) scales are most commonly used , such as the QLQ-C30, a score for cancer patients that is divided into five domains, namely: physical, functional, cognitive, emotional and social (McBain *et al.*, 2021). The EORTC BN20 score is a questionnaire developed specifically for patients with central nervous system neoplasia, still in development, but widely used (Hanna *et al*., 2020). Some other questionnaires are used less frequently, such as the FACT- Br, which is more used in patients with brain metastases (Lim, Xia, Bettegowda & Weller, 2018; Campos et al., 2021; McBain *et al.*, 2021; Hanna *et al*., 2020; Chiu *et al*., 2012).

Faced with the lack of clarity and concreteness of information on quality of life in the treatment of glioblastoma in the last 30 years, associated with the great disparity of methods for its evaluation, this work proposes to carry out a systematic review of the literature to gather and synthesize the information on the subject in the last thirty years, after the introduction of chemotherapy with temozolomide.

2. Methodology

A systematic review of the literature was carried out, with a search in the bibliographic database of PubMed, Medline and Lilacs, with guidance according to the PICO methodology (patient/participants, intervention, control and outcomes) (Santos et al., 2007). In the first component – P patients and problems – the group of patients with glioblastoma in its different stages, male and female, without age restriction was determined. Regarding item I, the intervention evaluated was the use of temozolomide, associated or not with different therapies such as radiotherapy and surgery, while the control group referring to item C of the protocol was determined as any therapy for glioblastoma that does not involve the use of temozolomide. Finally, the primary outcome evaluated was the change in quality of life through the different scales presented in the trials and studies.

The list of studies included was clinical trials, systematic reviews and meta-analyses that included patients with glioblastomas, in their different stages of development, regardless of age, sex or ethnicity, as participating individuals, whose intervention was the use of chemotherapy with of temozolomide, whether or not associated with surgical and radiotherapy, regardless of the number of sessions and dose.

The terms glioblastoma (DecS identifier 31846), temozolomide (DecS identifier 57539) and life quality (DecS identifier 12225) were used, based on a query in the DecS and MESH health descriptors, with association through AND and OR determinants. Articles were selected from the last available date, 1990, to the date of consultation. Eligibility criteria were full text availability; as for methodology, clinical trial, randomized clinical trial, meta-analysis and systematic review were chosen.

The exclusion criteria adopted were the tangency of the theme: non-assessment of quality of life or non-use of temozolomide. Studies that evaluated temozolomide against different controls were maintained: standard therapy of

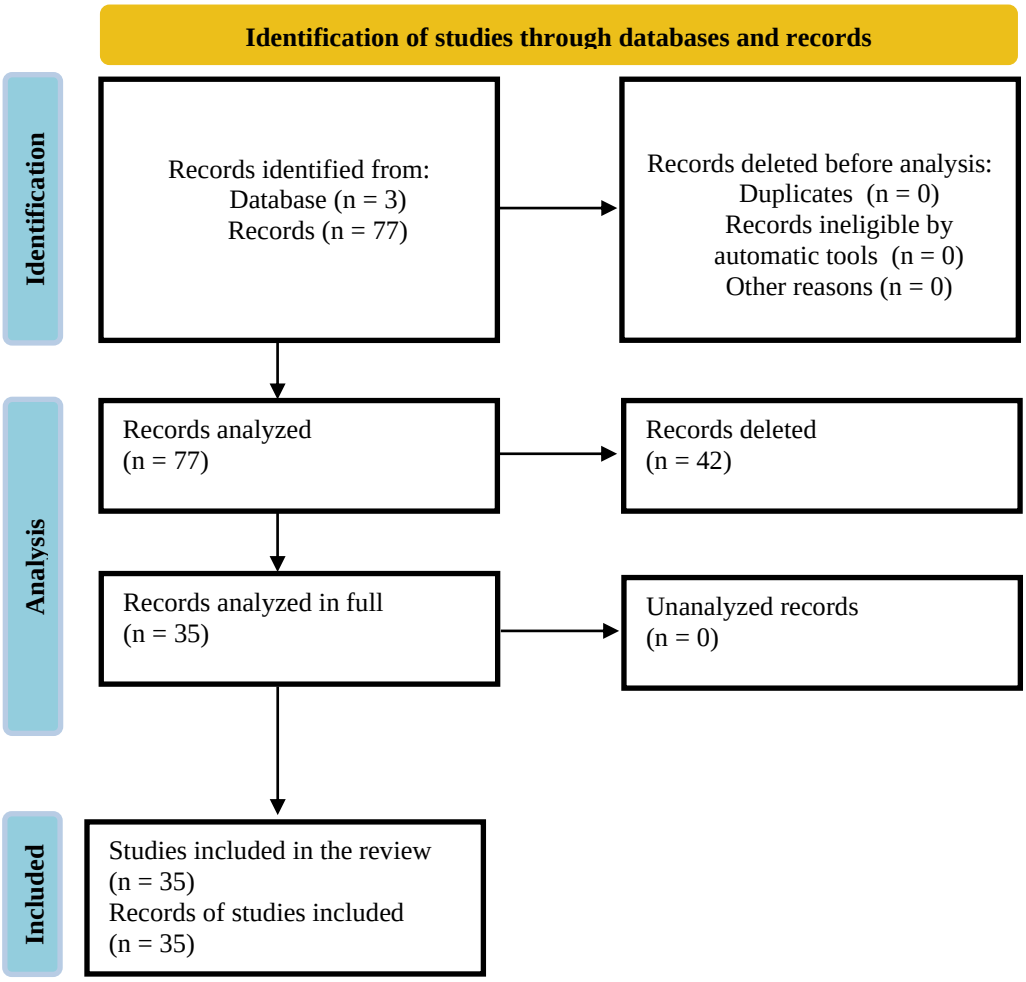
radiotherapy alone, different chemotherapy drugs and different forms of administration and association between chemotherapy and radiotherapy.

Once the aforementioned criteria for research, inclusion and exclusion of studies were determined, the PRISMA (Page *et al.*, 2021) flowchart was used, as available for systematization of the analysis, as described in Figure 1.

After selecting the studies, a qualitative systematic analysis was performed with data stratification in the following categories: study model, sample characteristics, quality of life as a primary or secondary outcome, scales used and effect on quality of life.

Initially, 77 studies were found, of which 42 were excluded according to the aforementioned criteria. Duplicates were also eliminated. Of the 35 studies analyzed, 27 were clinical trials, with a wide variety of conduction, most of them non-randomized and open-label; 3 were observational and longitudinal, constituting two cohorts and a case-control; 3 meta-analyses and 2 systematic reviews. The selection of studies is illustrated in Figure 1.

Figure 1 – PRISMA flowchart for analysis and selection of studies (Page *et al.*, 2021).



Source: Authors.

3. Results and Discussion

The results of the analysis and stratification of the articles are shown in Table 1, below.

Table 1 - Results of the individual analysis of each study.

Study	Model	Sample (age in years and performance index)	Primary / Secondary Outcome	Scale	Effect / conclusion
PAULSEN, Frank *et al.*, 1999.	Open single-center clinical trial .	Average 40 – 69 years / -	Total survival / -	-	-
OSOBA, BRADA, YUNG & PRADO 2000.	Observational, individualized, longitudinal, prospective.	Average 49 – 53 years / KPS > 70	Quality of life / -	EORTC QLQ-C30 and BCM 20	Increase in quality of life until time of disease progression
YUNG, WKA *et al*., 2000.	Multicenter, randomized, open-label, phase II clinical trial.	Average 52 years / KPS > 70	Survival / Quality of life	EORTC QLQ-C30 and BCM 20	Improved quality of life compared to procarbazine until time of disease progression
BRADA, M. *et al.* , 2001.	Clinical, multicenter, open, uncontrolled trial.	Average 54 years / KPS>70	Disease-free progression / Quality of life	EORTC QLQ-C30 AND BCM 20	Improvement in baseline quality of life prior to therapy, but not maintained after progression. Greater in the motor and social domain.
KHAN, Raja B. *et al*., 2002.	Clinical, single-center, open-label , non-randomized trial.	Average of 55 years / KPS > 70	Radiological response / Quality of life	FACT-BR	No statistically significant difference between the two groups.
DINNES, CAVE, HUANG & MILNE, 2002.	Systematic review	-	-	-	Better quality of life when compared to procarbazine
CHIBBARO, S. *et al.* , 2004.	Clinical, single-center , non-randomized, open - label trial.	Average of 57 years / KPS > 70	Safety and survival / Quality of life	KPS	Improved quality of life, secondary to an increase of approximately 10 in KPS
BRADA, Michael *et al*., 2005.	Phase II, multicenter, non-randomized, open-label clinical trial.	Mean age 55 years / WHO PS > 2	Disease-free progression / Quality of life	-	Although it cites changes in quality of life, it does not make an assessment using a scale, nor does it explain the results.
TAPHOORN, Martin JB et al., 2005.	Clinical, randomized, multicenter trial.	Average 55 years / -	Primary survival / Quality of life	EORTC QLQ-C30 AND BN20	No statistically significant difference between the two groups
HAMILTON, David A., 2006.	Clinical, multicenter, controlled trial.	18 to 70 years / WHO OS < 2	Primary quality of life / -	EORTC QLQ-C30 AND BN20	No statistically significant difference between the two groups.
CAROLI, Manuela *et al.* , 2007.	clinical trial	Average 58 – 60 years / average KPS of 70	Mean survival / KPS and MMSE	KPS and MMSE	Improved quality of life by increasing KPKS and MMSE in the group with early use of temodal
MINNITI, Giuseppe *et al.* , 2009.	Prospective non-randomized clinical trial	Average of 73 years / average KPS of 70	Average survival / Quality of life	EORTC QLQ-C30	Global quality with no statistically significant change; physical, social domain and fatigue worsened from baseline
KOCHER, Martin *et al.* , 2008.	Multicenter, randomized clinical trial	Average of 58 years / -	-	EORTC QLQ-C30	It indicates an increase in the quality of life in the radiotherapy and temozolomide association group , however the study was terminated before being concluded
KONG, Doo- Sik *et al*., 2010.	Clinical trial, single center , open	Average of 51 years / KPS > 70	Disease-free progression / Quality of life	SF-36	Reduced quality of life in the physical domain; lack of significance in mental health
MALMSTRÖM, Annika *et al.* , 2012.	Clinical, multicenter, randomized trial	Mean age 70 years / WHO PS < 2	Overall survival / -	-	Quality of life data not evaluated
MINNITI, Giuseppe *et al.*,	Prospective non-	Average of 73 /	Overall survival /	EORTC QLQ-	Increase in the overall quality

2013.	randomized clinical trial	average KPS of 70	Quality of life	C30 AND BN20	of life, justified by an improvement in the social and cognitive component; no changes in communication and insomnia; fatigue worsens.
REDDY, Krishna *et al.*, 2013.	Phase II clinical trial	Average of 60.5 years / average KPS of 80	Primary quality of life / -	EORTC QLQ-C30 AND BN20	Lack of statistical significance in overall quality of life
YIN, An-an *et al.*, 2013.	Systematic review	-	-	-	Absence of evaluation by standardized scales
ARMSTRONG, Terri S. *et al.*, 2013.	Phase 3 , multicenter, randomized clinical trial	Average of 58 years / KPS > 90	Overall survival / Quality of life	EORTC QLQ-C30 AND BN20	Although differences in the physical domain, without statistical significance in the overall quality of life
YIN, An-an *et al.*, 2014.	Meta -analysis of clinical trials	-	-	-	It points to improvement in the physical, emotional and cognitive domains, but without changes in the overall quality of life
TAPHOORN, Martin JB *et al.*, 2015.	Phase III, multicenter, double-blind, placebo-controlled clinical trial	Average of 56 years / -	Disease-free progression / Quality of life	EORTC QLQ-C30 AND BN20	There was no clinically relevant change in quality of life in both study arms.
PERRY, James R. *et al.*, 2017.	Randomized, multicenter clinical trial	Average of 73 years / ECOG > 2	Average survival / Quality of life	EORTC	Similar results between the two study groups
BADRUDDOJA, Michael A. *et al.* , 2017.	clinical trial	Average of 53 years / average KPS of 83	Survival / Quality of life	FACT BR	Lack of statistical significance
ZHU, Jay- *Jiguang et al.*, 2017.	Phase III, multicenter, randomized clinical trial	Average of 57 years / Average KPS of 90	Average survival / quality of life	EORTC QLQ-C30 AND BN20; MMSE and KPS	Initially, there was improvement in the group with association between TMZ and treatment fields, but it was not maintained after 9 months of progression
SCHÄFER, Niklas *et al.* , 2018.	Randomized, multicenter, controlled, open - label clinical trial	Average of 56 years / -	Disease-free progression / Quality of life	EORTC QLQ-C30 AND BN20	No significant difference between groups
TAPHOORN, Martin JB *et al.*, 2018.	Multicenter, open-label, randomized clinical trial	Average of 54.8 years / average KPS of 90	Survival / Quality of life	EORTC QLQ-C30 AND BN20	No significant difference between groups, despite dermatitis in the group with treatment field
REYES-BOTERO, German *et al.*, 2018.	Multicenter, non-randomized, open-label, phase II clinical trial	Average of 76 years / average KPS of 60	Survival / Quality of life	EORTC QLQ-C3O and BN20	Improved quality of life and cognition in the group treated with temozolomide and bevacizumab
LOMBARDI, Giuseppe *et al.* , 2018.	Observational, prospective, unicentric	Average of 65 years / KPS > 70	Quality of life / -	EORTC QLQ-C30, BN20, MMSE and HADS	Clinical and statistical improvement in the emotional domain, others remained without significant changes
PEDRETTI, Sara *et al.*, 2019.	Phase II, randomized clinical trial	Over 50 years old / -	Survival / Quality of life	NSS	Higher quality-adjusted survival in the radiotherapy-only group
WELLER, Johannes *et al.* , 2019.	Multicenter, randomized, open - label clinical trial	18 to 70 years / KPS > 70	Primary quality / -	EORTC QLQ-C30, BN20, MMSE and NOA- 7	No clinical and statistical difference between groups – with and without lomustine
HANNA, Catherine *et al.* , 2020.	Meta-analysis	Advanced age / -	-	-	Apparent worsening in the communicative domain in patients undergoing radiotherapy , but with poor analysis due to loss of patients

MCBAIN, Catherine *et al.* , 2021.	Meta-analysis	-	Tumor recurrence / -	-	Data on quality of life not solid
MIR, Taskia ; POND, Gregory; GREENSPOON, Jeffrey N., 2021.	Observational, retrospective, longitudinal	Average of 73 – 74 years / average KPS of 70 / average MMSE of 27	-	KPS and CTCAE	Absence of objective analysis on quality of life
ARAKAWA, Yoshiki *et al.* , 2021.	Multicenter, randomized, phase III clinical trial	Over 70 years / -	Survival / Quality of life	EORTC QLQ-C30 AND BN20	No data yet.

Source: Authors.

Among the studies, 7 evaluated samples aged over 70 years and with lower performance indexes, either through the KPS below 70 points, or different scales, such as the World Health Organization – WHO PS; apart from the reviews and meta-analyses, the other studies were guided by individuals younger than 70 years and with better performance indices.

Regarding the intent of the outcome, six studies, although mentioning quality of life, did not explain or perform analysis, either primarily or secondarily, either due to lack of objective use of scales or loss of patients during follow-up. Five studies performed analysis as a primary intent, 21 as a secondary outcome, and four did not make it clear, even if they did analysis.

Among the scales used, a predominance of EORTC QLQ-C30 and BN20 (20 studies) was observed, followed by the mini mental state examination (MMSE - 5 studies), KPS (4 studies), FACT- Br (2 studies), HADS (1 study), NSS (1 study), CTCAE (1 study) and NOA-7 (1 study).

Regarding the impacts on quality of life, improvement was found in some studies (Osoba, Brada, Yung & Prado, 2000; Yung *et al.*, 2000; Brada *et al*., 2001; Dinnes, Cave, Huang & Milne, 2002; Chibbaro *et al*., 2004; Minniti *et al*., 2013; Zhu *et al*., 2017; Reyes-Botero *et al*., 2018). In the remaining studies, only improvement in isolated domains that were not clinically reflected or lack of statistical significance was reported, or there was no direct analysis of quality of life (Paulsen *et al*., 1999; Khan *et al*., 2002; Brada *et al*., 2005; Taphoorn *et al*., 2005; Hamilton, 2006, Minniti *et al*., 2009; Kocher *et al*., 2008; Kong *et al*., 2010; Malmstrom *et al*., 2012; Reddy *et al*., 2013; Yin *et al*., 2013; Armstrong *et al*., 2013; Yin *et al*., 2014; Taphoorn *et al*., 2015; Perry *et al*., 2017; Badruddoja *et al*., 2017; Schafer *et al*., 2018; Taphoorn *et al*., 2018; Lombardi *et al*., 2018; Pedretti *et al*., 2019; Weller *et al*., 2019; Mir, Pond & Greenspoon, 2021) .

Even if in some works, such as Kocher 's *et al*. (2008), an increase in quality of life was initially observed, the data could not be analyzed with methodological rigor, with the main obstacle being the loss of patients or the progressive inability to fill in the scales, or even due to the non-completion of the study (Arakawa *et al*., 2021) .

The insertion of temozolomide in the treatment of glioblastoma generated a new paradigm in neuro-oncology, opening possibilities for isolated treatment and in association with surgery, radiotherapy or other chemotherapeutic agents. The discovery of MGMT and its methylated variant, which is more sensitive to temozolomide, has also raised expectations for changes in the treatment of this condition (Wirsching et al., 2016; Braun & Ahluwalia, 2017).

Although research initially focused on younger patients with a good performance profile – non-preferential distribution of disease onset, trials with patients over 70 years of age and with lower performance indices appeared in greater numbers in the last decade (Braun & Ahluwalia, 2017; Minniti *et al*., 2009).

Disregarding the increase in survival, which is variable, but with a modal interval between 2 and 4 months (Brada *et al*., 2001; Caroli *et al*., 2007; Minniti *et al*., 2013; Perry *et al*., 2017), the overall quality of life remained unchanged with the use of temozolomide , an important fact for bioethical analysis because the therapy is non-inferior, a condition that must be

taken into account in the scope of public health, especially the cost-benefit and ethical relationship, regarding the point of prolonging a life without quality, classified according to some authors as dysthanasia (Sim, Nowak, Lwin & Khasraw, 2021).

Dysthanasia can be understood as a protracted, suffering and painful process resulting from exaggerated and disproportionate actions to prolong a patient's life (Pessini, 2009). It is not restricted to the patient, but also to family members, caregivers, the health team and surroundings. In this scenario, the debate is inevitable – by not providing an improvement in quality of life, does the use of temozolomide constitute dysthanasia?

While not increasing the quality of life can be understood as prolonging life without adding benefits, understood as dysthanasia , on the other hand, by not adding major negative adverse effects and not decreasing quality of life , it can be seen as neutral and not inferior to the current modalities – surgery and radiotherapy (Braun & Ahluwalia, 2017; Davis & Mulligan Stoiber, 2011).

It is not within the scope of the present study to resolve or resolve this issue, but rather to point out one more reason for a greater focus on the analysis of quality of life in clinical trials that address the therapy of glioblastoma.

New therapies and associations have emerged, such as immune therapy through “vaccines” indicated by Lim *et al.* (2018), taking advantage of the observed paradoxical effect of temozolomide -associated lymphopenia to lead to an increase in the immune response directed to tumor antigens.

Among the immunobiological therapies, bevacizumab, an anti-VEGF monoclonal antibody, which acts by blocking neoangiogenesis and consequent tumor nutrition, stands out. Despite the great theoretical development regarding the immune response in glioblastomas, there was no practical impact on the patients ' quality of life (Karachi et al., 2018; Lim et al., 2018).

The use of scales is not standardized and, although not validated in all countries, the European scales EORTC QLQ-C30 and BN20 were the most frequent and proved to be the most homogeneous and solid way of analyzing quality of life, through stratification into domain-specific and global, as reinforced by Domenech , Hernandez and Halana (2021) and Reddy *et al.* (2013), in addition to presenting greater specificity for glioblastomas when compared to general tools such as the Mini Mental State Examination (MMSE) and the isolated use of the Karnofsky Performance Scale (KPS).

The high rate of loss to follow-up, secondary to rapid disease progression and low patient survival, compromises the collection and analysis of data, as observed in Kocher's work (2008). In a more recent work, Arakawa *et al* (2021) , there is still no availability of data and analysis, even if objectified in the methodology.

The analysis of changes in quality of life in most trials has limited space and, even when objectified, does not present conditions of rigorous methodological conduct, mainly due to the sample profile and disease progression, with a high loss of index cases (Kocher *et al*., 2008; Minniti *et al*., 2013; Domenech et al., 2021; Campos et al., 2021).

Methodological obstacles are frequent, given the complexity of the assessment due to the lack of standardization and heterogeneity of scales, high rate of loss of patients and follow-up, but which must be circumvented in order to obtain a more reliable analysis.

The knowledge of quality of life in a baseline, with and without the use of temozolomide is important for determining the status quo, an initial step to then proceed to analyzes of superiority, non-inferiority and even cost-benefit analysis of each new drug therapy and association, a condition that requires solid and comprehensive data (Lukas et al., 2021).

4. Conclusion

Despite the combination therapy with temozolomide, overall survival remains low and recent advances in understanding the pathological entity have not translated into concrete benefits in the quality of life and survival of patients.

Although some works showed changes in specific domains, with emphasis on the improvement of quality of life in the physical, social and cognitive domains, when extrapolated analysis to the global component, there was no significant evidence of improvement.

Although initially most trials were based on comparison with the standard therapy: surgery and radiotherapy, some associations emerged over the years, such as temozolomide with bevacizumab Such an association has not yet been shown to be significant in terms of overall quality of life compared to temozolomide alone, but with greater risks of important side effects such as immunosuppression.

In view of the qualitative analysis of the review, the absence of improvement in quality of life with the use of temozolomide in patients with glioblastoma is evidenced.

Thus, it is necessary to carry out quantitative studies with adequate methodology-such as meta-analyses, to evaluate the data available in the EORTC QLQ-C30 and BN20, in order to confirm the scores.

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