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Prognosis of patients with newly diagnosed glioblastoma treated with molecularly targeted drugs combined with radiotherapy vs temozolomide monotherapy

A meta-analysis

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Abstract

Background: Glioblastoma (GB) is one of the most common malignancies with limited standard therapies such as surgery, radiotherapy (RT) plus temozolomide (TMZ). Molecularly targeted drugs have been investigated among various clinical trials and are expected to develop in the field of tumor therapy, while the efficacy remains uncertain due to limited previous results. Thus, we focus on the evaluation of molecularly targeted drugs to clarify its overall effectiveness in terms of treating newly diagnosed GB.

Methods: Electronic databases were searched for eligible literatures updated to April 2018. Randomized-controlled trials were included to assess the efficacy and safety of molecularly targeted drugs in patients with newly diagnosed GB. The main outcomes were further calculated including the following parameters: PFS (progression-free survival), OS (overall survival) as well as AEs (adverse events). All data were pooled along with their 95% confidence interval using RevMan software. Sensitivity analyses and heterogeneity were evaluated quantitatively.

Results: The combination of molecularly targeted drugs with TMZ+RT had no significant effects on OS (OR=0.96, 95%CI=0.89−1.04, $P=.36$). Meanwhile, the combination regimen significantly improved the PFS of patients with newly diagnosed GB (OR=0.86 ,95% CI 0.75−0.98, $P=.02$). The rate of AEs (OR=1.68,95%CI=1.44−1.97, $P<.00001$) was higher in patients receiving molecularly targeted drugs, which was comparable to the contemporary group.

Conclusion: Longer PFS and a higher rate of AEs were observed with the addition of molecularly targeted drugs to standard chemoradiation in patients harboring newly diagnosed GB. Nevertheless, compared with the control arm, the regimen did not significantly prolong OS.

Abbreviations: AEs = adverse events, GB = Glioblastoma, OS = overall survival, RT = radiotherapy, TMZ = temozolomide, VEGF = vascular endothelial growth factor.

Keywords: molecularly targeted drugs, newly diagnosed glioblastoma, radiotherapy, temozolomide, treatment

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The authors report no conflicts of interest.

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1. Introduction

Glioblastoma (GB) is one of the most common life-threatening malignant tumor that affects patients' central nervous system.[1] Poor prognosis exists among patients with a median survival rate of about 1 year with treatment and reference in the main text either the US (CBTRUS) or UK (Glioblastoma in England: 2007–2011) data after clinical diagnosis due to the aggressive feature of neoplasms.[2]

Maximal safe resection has been regarded the best standard treatment available currently for newly diagnosed GB, followed by concomitant radiotherapy (RT) combined with oral alkylating agent temozolomide (TMZ), as well as maintenance therapy with TMZ (TMZ/RT+TMZ),[3–4] which offers the median survival rates of 14 to 16 months.[5] The prognosis of GB patients remains very poor although the standard therapies (maximal safe resection followed by TMZ and RT) were conducted.[2,6]

Many attempts have been tried to explain the underlying biology of oncogenesis as well as the molecular mechanisms of GBM that may be responsible for the aggressive phenotype of this

malignancy, in order to further determine the potential clinical use for diagnosis. Molecularly targeted drugs are one of the main medical treatments for cancer, which are expected to be personalized therapy to identify individual tumors at the molecular level. Therefore, immunotherapeutic strategy may be a valid therapy for cancer. It contributes especially to bringing a new understanding of molecular pathways for gliomagenesis and becomes part of the standard neuro-pathological evaluation of GB.[7]

GB is characterized by overexpression of vascular endothelial growth factor (VEGF), which could promote oncoangiogenesis and take an active part in tumor growth as well as progression.[8–10] In addition, EGF receptor (EGFR) signaling with EGFR amplification is one of the mechanisms whereby GB causes radioresistance[11–12] and chemoresistance,[12] which may play a vital role as a mediator. Thus, it is always pivotal to understand the molecular mechanisms of tumor-mediated immunosuppression as well as tumor-associated angiogenesis, which provides significant foundation for a new generation of molecularly targeted drugs and therapy.

Here, we focus on molecularly targeted drugs for newly diagnosed GB based on reasonable clinical options. A meta-analysis was conducted to demonstrate and further assess the overall efficacy of molecularly targeted drugs.

2. Materials and methods

2.1. Ethical statement

Ethics approval was waived because this study did not involve any human participants or animals.

2.2. Search strategy

Two investigators independently searched electronic databases: PubMed, Embase, and the Cochrane Library up to April 2018. We searched for all randomized clinical trials for evaluating the value of molecularly targeted drugs in patients with newly diagnosed GB. The process was established to identify all articles with the keywords "chemotherapy " "bevacizumab" "dasatinib" "nimotuzumab" "cilengitide" AND "glioblastoma" AND "newly diagnosed" AND "efficacy". Medical Subject Heading (MeSH) terms that were associated with the current meta-analysis were also searched. The reference lists of all articles that dealt with the topic of interest were manually searched to check for additional relevant publications.

2.3. Eligibility criteria

Studies that met the following mentioned criteria were included in the present meta-analysis:

(1) studies were designed as randomized controlled trials (RCTs) with newly diagnosed GB;
(2) studies designed to compare the efficacy of molecularly targeted drugs combined with TMZ/RT+TMZ and TMZ/RT +TMZ alone;
(3) the outcomes of interest were available regarding efficacy (survival) and safety (adverse events (AEs)), and hazards ratio (HR) with corresponding 95% CIs were provided;
(4) only full texts were included.

Studies that failed to meet the above-mentioned inclusion criteria should be excluded from this meta-analysis.

2.4. Quality assessment

As recommended by The Cochrane Handbook for Systematic Reviews of Interventions, we used the Jadad 7-item scale to assess the quality of the current study as well as the overall methodological quality of RCTs.

2.5. Data extraction

Two reviewers conducted and evaluated data extraction separately. Any arising disagreement was resolved by consensus. The main categories from selected studies were based on the following items: family name of first author, year of publication, mean age, therapeutic design, sample size, and outcomes of interest (AEs, PFS, and OS). The corresponding HR along with 95% CIs was utilized to describe main outcomes of the studies, respectively, including survival (PFS and OS) as well as AEs, and 95% CI was calculated for each estimate.

2.6. Statistical analysis

In the current meta-analysis, 1[26] study provided no data on HRs or 95% CIs, and all the available data were in the form of Kaplan-Meier (K–M) curves. Survival data were extracted from the form of the K–M survival curve according to the methods by Tierney JF.[13] The I^2 statistic test was performed to further examine statistical heterogeneity between the trials.[14] Heterogeneity was examined through the I^2 statistic, describing as follows: low, 25% to 50%; moderate, 50% to 75%; or high, >75%.[15] We applied the fixed-effects model if the studies were of low heterogeneity. In other cases, we used the random effects model.

All analysis was conducted through the use of Review Manager version 5.3 software (Revman; The Cochrane Collaboration Oxford, United Kingdom). Studies with a P value less than .05 was thought to have statistical significance. Forest plots showed the findings of our meta-analysis. Begg test and the Egger test were conducted to evaluate publication bias.

3. Results

3.1. Search results and study characteristics

A total of 324 studies were retrieved initially for evaluation. Based on the criteria described in the methods, 18 publications were evaluated in more detail, but some did not provide enough detail of outcomes of 2 approaches. Therefore, a final total of 14 RCTs[16–29] assessing the value of molecularly targeted drugs among patients harboring newly diagnosed GB were included. The search process is described in Figure 1.

All included studies in this meta-analysis were based on evidence with moderate to high quality. Table 1 describes the primary characteristics of the eligible studies in more detail.

3.2. Clinical and methodological heterogeneity

3.2.1. Pooled analysis of PFS comparing the addition of molecularly targeted drugs with the control group. The pooled data showed that the addition of molecularly targeted drugs achieved advantage in PFS vs the control group (Fig. 2), with the pooled OR being 0.86 (95% CI 0.75–0.98, $P=.02$).

3.2.2. Pooled analysis of OS comparing the additional use of molecularly targeted drugs with the control group. The pooled OS data from 14 studies showed that the additional use of

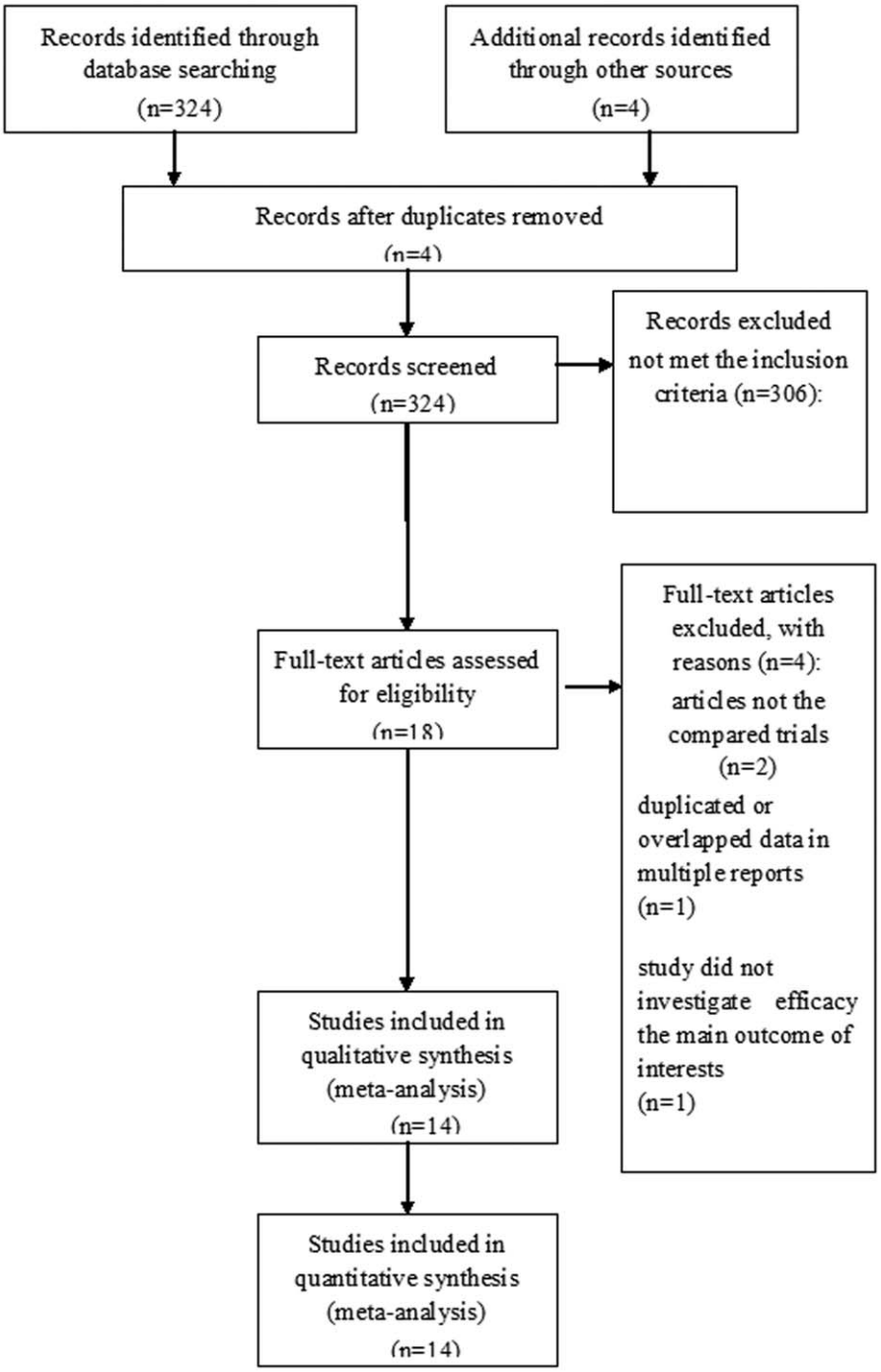

Figure 1. PRISMA flow chart of the selection process to identify studies eligible for pooling.

molecularly targeted drugs was not associated with improved OS (OR = 0.96, 95%CI = 0.89–1.04, $P = .36$) vs the control treatment (Fig. 3).

3.2.3. Pooled analysis of AEs comparing the addition of molecularly targeted drugs with the control group. Overall, 6 studies that reported data on AEs are shown in Figure 4. The pooled data showed that the addition of molecularly targeted drugs increased the risk of AEs of newly diagnosed GB patients (OR = 1.68,95%CI = 1.44–1.97, $P < .001$). (Fig. 4)

4. Discussion

GB is an aggressive refractory brain tumor with poor prognosis despite the best available therapy: maximal safe surgical resection, and RT combined with alkylating agents.[3] Standard treatment consists of TMZ/RT+TMZ for patients with newly diagnosed GB, which contributes to the improvement of OS vs the historical cohorts with standard therapy alone.[30–31]

GBM has been shown with multistep tumorigenesis ability according to some of the previous researches. The further

Table 1

The primary characteristics of the eligible studies in more detail.

Study	Age		Cases		Treatment	
	Experiment	Control	Experiment	Control	Experiment	Control
Gilbert 2014	312	309	312	309	BE+RT+TMZ	RT+TMZ
Chinot 2014	57	56	458	463	BE+RT+TMZ	RT+TMZ
Chauffert 2014	60.2	60.9	60	60	BE+RT+TMZ	RT+TMZ
Herrlinger 2013	56	56	116	54	BE+RT+TMZ+IRI	RT+TMZ
Balana 2016	62.9	62	48	45	BE+RT+TMZ	RT+TMZ
Stupp 2014	NA	NA	272	273	Cil + Rad + Tem	RT+TMZ
Westphal 2015	55	56	75	74	Nim+Rad+Tem	RT+TMZ
Nabors (1) 2015	55.6	57.7	88	89	Stand Cil+Rad+Tem	RT+TMZ
Nabors (2) 2015	56	57.7	88	89	Intensive Cil+Rad+Tem	RT+TMZ
Albert Lai 2011	57.4	59.4	70	110	BE+RT+TMZ	RT+TMZ
Laack 2015	NA	NA	NA	NA	Das+RT+TMZ	RT+TMZ
Lee 2015	59	55	70	36	Vandetanib+RT+TMZ	RT+TMZ
Wick 2014	NA	NA	NA	NA	TEM+RT+TMZ	RT+TMZ
Chinnaiyan 2017	NA	NA	88	83	Everolimus+RT+TMZ	RT+TMZ
Wakabayashi 2018	61	61	59	63	TMZ+IFNβ+RT	RT+TMZ

BE = bevacizumab, Cil = Cilengitide, Das = dasatinib, GB = Glioblastoma, NA = not available, Nim = nimotuzumab, OS = overall survival, PFS = progression- free survival, RT = radiotherapy, Tem = temozolomide, TMZ = temozolomide.

understanding of the molecular mechanisms of GBM ushered in a new generation of molecularly targeted drugs. Targeted drugs block the growth of cancer cells by interfering with specifically targeted molecules that are necessary for tumor growth.[32]

A great number of molecularly targeted drugs have been explored and successfully developed with high specificity and favorable effects to treat cancer over the past decades.[33–35] Subsequently, substantial efforts have been made among several trials in expectation of bringing the beneficial outcomes of molecular targeted drugs in clinical practice such as treating newly diagnosed GB accompanied with TMZ/RT+TMZ.[21] It was found that molecular classification schemes can separate GBM into clinically relevant subgroups in molecular neuropathology, while it was a homogeneous group of tumors based on histologic criteria essentially.[36–37]

Several RCTs have been performed in order to validate bevacizumab's efficacy in both first- and second-line therapy, but controversial results existed regarding OS as well as PFS. Other antiangiogenic drugs, including dasatinib (PDGF receptor tyrosine kinase inhibitor), everolimus (mTOR inhibitor), cilengitide (targeting integrins αvβ3, αvβ5, andα5β1), and cediranib and valatinib (VEGF receptor tyrosine kinase inhibitors) were investigated among several RCTs.

Taken together, no significant difference was found in OS with the molecularly targeted drugs for newly diagnosed GB but with longer PFS in these patients. What is more, the incidence of severe AEs was higher with the molecularly targeted drugs than the standard treatment.

The improvement of PFS by molecularly targeted therapy could be associated with the aggressive feature of GBMs. According to a preclinical study, bevacizumab is thought to have the ability to induce the expression of matrix metalloprotease-2 in invasive tumor phenotype.[38] Another explanation is that the imaging bias led to improved PFS. The molecularly targeted drugs, such as bevacizumab, could stabilize the blood-brain-barrier and minimize the ability of the MRI contrast agent gadolinium to reach the tumor, thus "improved" or "cleaner" MRIs and pseudo-response were shown. Considering that the

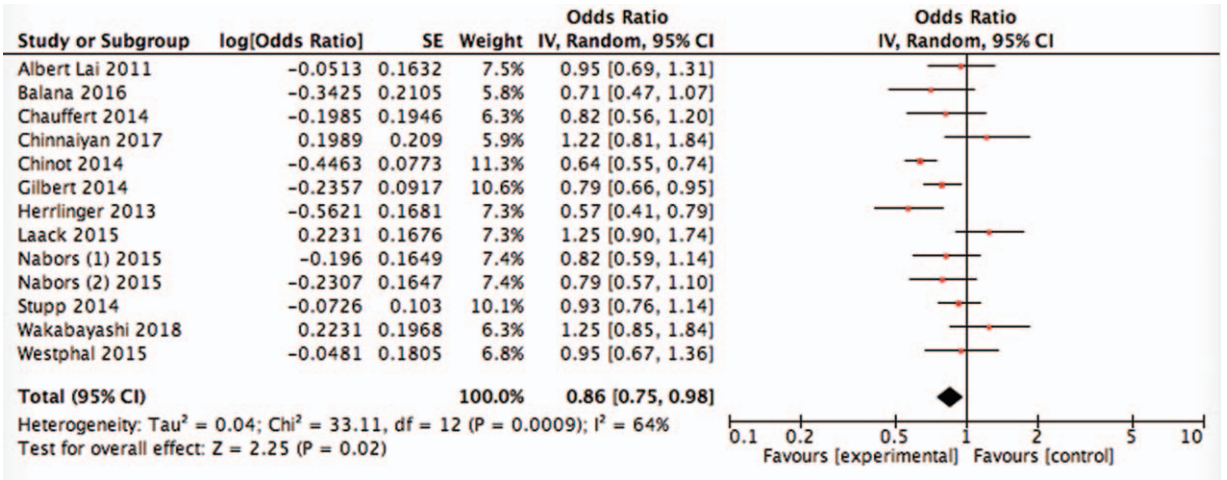

Figure 2. Pooled analysis of progression-free survival comparing the addition of molecularly targeted drugs with the control group.

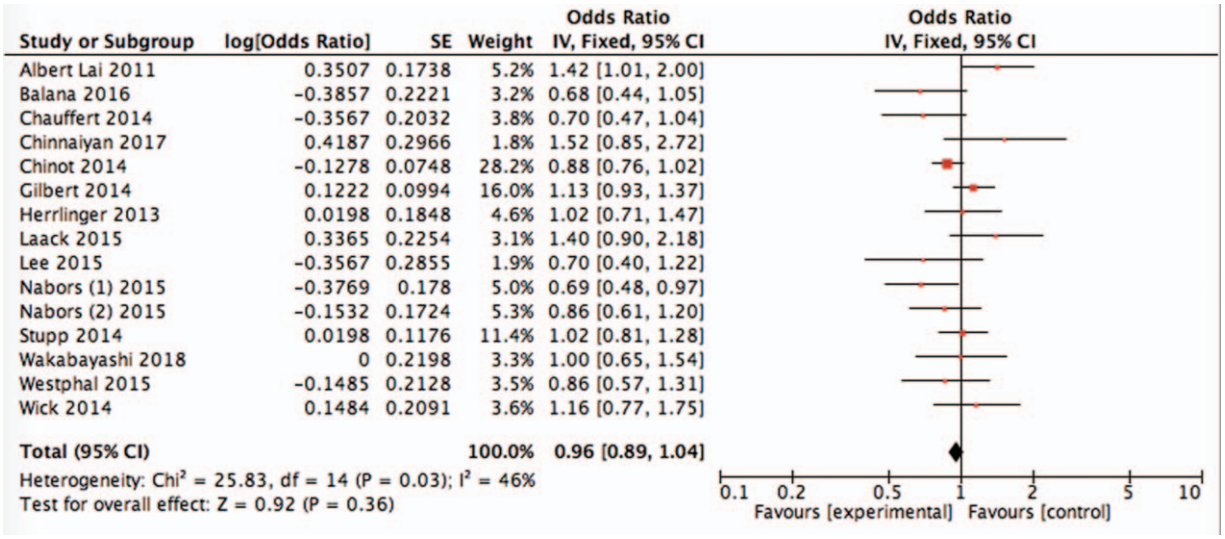

Figure 3. Pooled analysis of overall survival comparing the addition of molecularly targeted drugs with the control group.

pseudo results of progression could not be avoided through magnetic resonance, the potential imaging bias existed with the delay in diagnosing progression (a largely radiographic diagnosis) and consequently led to prolonged PFS.[39]

Given that the cross-experiment design of various studies could interfere with potential survival advantages, PFS improvement was not accompanied with OS prolongation. Of note, the effects of second-line crossover therapy may contribute to the discrepancy, and the AVAglio trial indicated the prolonged data in both PFS and OS with the additional use of bevacizumab to standard GBM treatment for patients with only single line therapy.[40] Moreover, drug resistance was another important factor that affects the overall efficacy of molecularly targeted drugs for newly diagnosed GB.

The quality of life as well as the prognosis of GBM patients could be affected due to theAEs of targeted drugs. According to our meta-analysis, the risk of adverse vascular events was increased among patients harboring newly diagnosed GBM who had been treated with molecularly targeted drugs. As reported by these trials, the most common AEs included lymphopenia and thromboembolic events, and were directly associated with molecularly targeted drugs.[18–19,21,29]

Considering the importance of AEs that may have great influence on patients, efforts were expected to be made to identify a specific molecular subtype that predicts response accurately, and hence, to offer strong evidence in subsequent clinical trials in search for alternative strategies in order to gain therapeutic benefit from molecularly targeted therapeutic agents.

This systematic analysis has several limitations that should be discussed. First, this study was a study-level meta-analysis; due to the lack of patient-level data, and data was pooled from different studies with different drug treatments, clinical heterogeneity among trials should be taken into consideration in the interpretation of our findings. Second, as the data of molecular subtype in the included trials was limited, we did not perform subgroup analysis of survival in this meta-analysis.

5. Conclusion

The combination of molecularly targeted therapeutic with standard therapy showed favorable outcomes in PFS, but the superiority of molecularly targeted therapeutic to standard therapy in OS was not demonstrated. The relevant effects could be limited due to the intervention of primary therapy based on the data of crossover therapy. One of the possibilities is that lack of prolonged OS may be caused by effective crossover treatment. In addition, despite the increased rate of AEs associated with molecularly targeted therapy was observed in the present study,

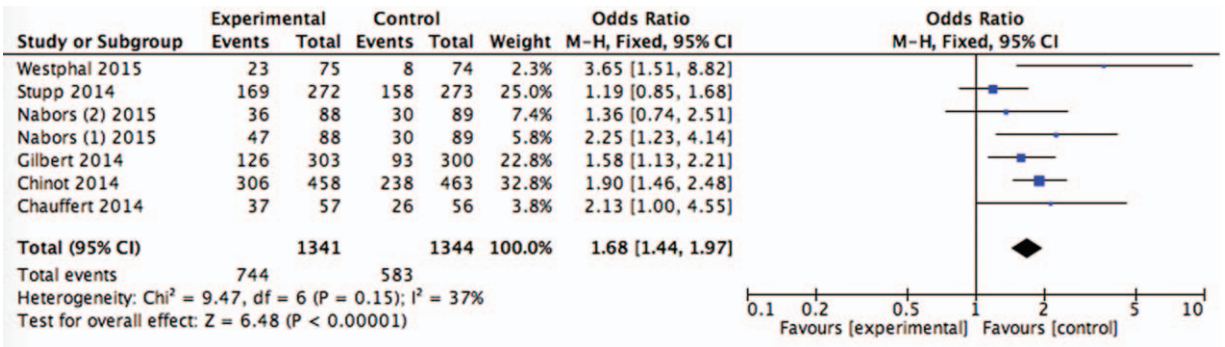

Figure 4. Pooled analysis of adverse events comparing the addition of molecularly targeted drugs with the control group.

even better quality of life quality with a stable condition was gained in GBM patients. Further studies will focus on searching for the best therapy with beneficial outcomes while minimizing toxicities for patients with various complications.

Author contributions

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