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CLINICAL EXPERIENCES WITH TEMSIROLIMUS IN GLIOBLASTOMA MULTIFORME; IS IT PROMISING? A REVIEW OF LITERATURE

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Abstract – *Background:* *Glioblastoma multiforme (GBM) is the most frequent, aggressive and incurable central nervous system (CNS) tumor. Despite conventional treatments such as surgery, radiotherapy and chemotherapy, there is no definite treatment for this disease. In recent years, temsirolimus has been evaluated in clinical studies as a suggested treatment for GBM.*

Material and Methods: *A review of literature within PubMed, Web of Science, Scopus and Google Scholar has been conducted through clinical studies, which assessed temsirolimus in GBM patients, up to July 2016. In this regard, the studies that met the inclusion/exclusion criteria were selected. The common information of the studies was categorized in 2 tables; one for demographic information, therapy characteristics and response rate and the other table for temsirolimus safety profile in GBM patients. Further information was noted in separated topics.*

Results: *Total 103 citations were collected; after elimination of duplicate and applying inclusion/exclusion criteria, 9 citations selected. From overall 292 enrolled patients, no complete response was found. Treatment was well tolerated except in combining with targeted therapies; overall survival and Progression Free survival cannot show superiority to standard treatment as well.*

Conclusions: *The present study shows that insufficient concentration of temsirolimus in the CNS, escape metabolism pathways in tumor cells and also dose reduction in combination therapy led to the ineffectiveness of the treatment. In addition, concomitant use of agents that can improve the availability of temsirolimus and block parallel pathway of malignant cell metabolism was noted in most of the studies as future perspective.*

KEYWORDS: *Glioblastoma multiforme, Temsirolimus, GBM, m-TOR inhibitor, CCI-779.*

INTRODUCTION

Glioblastoma multiforme (GBM) or grade IV astrocytoma is the most malignant CNS tumor, which arises from glial cells and their precursors[1]. GBM is accounted for 46.1% of all malignant brain and spinal cord tumors and approximately 55.1% of gliomas. GBM incidence is 3.2 new cases per 100,000 populations per year. The central brain tumor registry of the United States (CBTRUS) estimates 11,890 GBM cases predicted in 2015 and 12,120 in 2016[2].

Short overall survival, recurrence after first treatment, and poor prognostic state, have been proven about GBM despite existing treatment[3]. There are three standard types of treatment for GBM: debulking with surgery, radiation therapy and chemotherapy, but none of these treatments is curative or improve its overall survival rates as expected[4,5]. With the current standard chemo radiotherapy, the estimated median progression-free survival (PFS) and overall survival (OS) for GBM patient are 7 and 15 months, respectively. Also, only 5.1% of these patients survive to five years[2].

Molecular markers, such as genetic loss on chromosomes 1p/19q, IDH gene mutations, epigenetic silencing of the methyl-guanine methyl transferase (MGMT) gene promoter, are new sec-

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ondary indices for diagnosis and treatment of gliomas. These markers are asso ciated with tumor responsiveness to definite types of chemotherapy agents and therapy outcomes[6,7]. Accordingly new version of WHO classification of gliomas used, these molecular markers in addition to histology, define tumor entities[8]. According to the clinical features and molecular parameters, GBM is categorized in three types by WHO: (I) isocitrate dehydrogenase (IDH)-wildtype, which is prevalent in about 90% of cases and corresponds with primary or de novo glioblastoma without any history of previous gliomas; (II) IDH-mutant, which corresponds secondary glioblastoma and results from tumor progression of a previously lower grade glioma; (III) NOS, refers to tumors which full IDH evaluation is not possible[8,9].

Finding molecular alteration in biological pathways of neoplastic cells creates a necessity for seeking novel treatments. One of the pathways that influence pathogenesis and progression of GBM is the mammalian target of rapamycin (m-TOR). Phosphatase and tensin homolog (PTEN) mutations in GBM cause abnormal high activity of the pathways of phosphatidyl inositide 3-kinases (PI3K), protein kinase B (PKB), and m-TOR in the tumor cells[10]. The mechanisms of action are shown in Figure 1, which is adapted from Hurtado-de-Mendoza et al[11]. PTEN is expressed at 78.5% of cases and PTEN mutation exists in 24% of IDH-wildtype GBM[12,8]. Homozygous deletion of 10q23/PTEN conducts a more aggressive tumor phenotype and establishes its potential prognostic/predictive value for glioblastoma patients, notably patients more than 45 years old[13].

Temsirolimus is an inhibitor of m-TOR that also showed anti-tumor effects in a wide range of different tumor histotypes in preclinical models[14]. In 2007, it was approved by American food and drug administration (FDA) for treatment of advanced renal cell carcinoma (RCC), based on its anti-tumor effect[15].

Regarding to m-TOR pathway effect on glioma cells, effect of temsirolimus on GBM has been recently evaluated in trials alone or in combination with other treatments. Recently, a published meta-analysis of anti-antigenic therapy for GBM, with only one temsirolimus study, did not show improvement in treatment outcomes[15]. The purpose of our study is to gather all other evidence from published clinical studies, along with the final result[16] of the mentioned study[17] , to evaluate different aspects of temsirolimus in GBM patients, i.e. clinical efficacy, safety, patients' quality of life and tolerability and find out whether we can draw a conclusion.

MATERIALS AND METHODS

Study Purpose and design

We performed a systematic assessment of temsirolimus use in glioblastoma multiforme (GBM) malignancy. We extracted the efficacy and safety of the temsirolimus in GBM patients with or without other treatments in the literature over the study period.

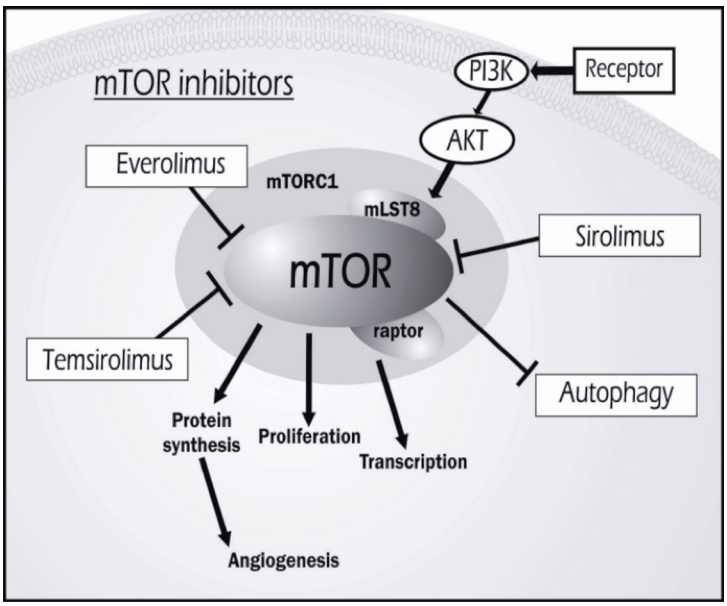

Fig. 1. mTOR Inhibitors mechanism of action.

Data sources and searched terms

Two authors performed a systematic, comprehensive search of literature within following databases; PubMed, Web of Science (WOS) and Scopus. Google scholar has been searched for any other remained citation from abovementioned databases. The search terms were "glioblastoma multiforme" or "GBM" or "grade IV astrocytoma" and "temsirolimus" or "CCI-779". These were searched in databases without applying any limitation or filters and in all fields. We also manually searched references within articles to identify additional studies. The search time span was up to July 2016.

Screening and Inclusion/exclusion criteria

All citations were imported into an EndNote X7 library. Duplicated records were eliminated first by software (matching the author, title, and publication year), next manually by authors.

Afterwards, two independent reviewers, MB and AM screened all the remained studies regarding their relevance to temsirolimus in GBM patients' treatment alone or in combination with other treatments. Studies were selected by their title and abstract and full-text whenever necessary.

We excluded studies performed on other than human, e.g. cell culture or animal models. All references other than the original studies were excluded: letters, case reports, abstracts, organizational reports, opinions or editorial papers and book chapters. Accordingly cross-sectional, case-control, clinical trial and cohort studies were only recruited. Articles in languages other than English were removed as well. Studies were also omitted if they were irrelevant; reviewers evaluated studies relevancy based on their provided information, i.e. reporting the treatment course, response rate and safety profile data.

Data extraction

The reported data from included articles were extracted and summarized in two tables, based on different articles' focal point.

In the primary section (Table I), sample size and patient demographic information (age, gender and race), study characteristics (article type, eligibility criteria), treatment details (temsirolimus dose, intervals and administration route), combination therapies (Chemotherapy agents and/or radiation) and efficacy parameters (response rate and survival) are reported. Section 2 (Table II) is allocated to evaluation of safety; the grade III and IV toxicities, temsirolimus dose modifications due to toxicities and other toxicity information.

RESULTS

Search result

One hundred and three references were found initially in aforementioned databases. After duplicates were eliminated, 97 references remained in our library. Through primary titles and abstracts screening, 16 relevant references were identified and after full-text appraisal of these 16 papers, 9 references were remained based on the inclusion/exclusion criteria to be reviewed (Figure 2).

Study characteristics

The entire 9 citations were trials; 2 phase I, 5 phase II studies and 2 studies were phase I/II. Time span of studies was from 2005 to 2016.

Totally 292 GBM patients were received temsirolimus in these studies, but the final evaluated patients, which completed the study course, were 280. Except 6 patients younger than 18, other were adults.

In most of the studies birth control usage and lactation avoidance were compulsory. Also normal organ functions including liver and kidney, normal hematologic indices, especially platelets and white blood cells were needed for participation in trials. Since hyperlipidemia is a proven adverse effect for temsirolimus, the normal lipid profile, defined as cholesterol<350 mg/dl and triglyceride<450 mg/dl, was also required.

One of our focal points was the disease characteristics and patient's performance situation, since they can affect the patients' outcomes[18,19]. Patients with recurrent GBM were included in 6 studies. In 3 other studies non-refractory and newly diagnosed GBM patients were also included. One of the most used patients' performance scales in included studies was Karnofsky performance scale (KPS) score, which applied in 4 studies and recruited patients with KPS≥ 60 (patient requires occasional assistance, but is able to care for most of his personal needs or have better performance). In another 3 studies, score up to 2 of eastern cooperative oncology group scale (ECOG) for patients was accepted that means the patient is ambulatory and capable of all self-care but unable to carry out any work activities (equal to KPS > 60-70)[20]. One study used Lansky scale to evaluate performance. The last one did not define any performance scale (Table I).

TABLE 1. Study characteristics and outcomes.

Reference	*Study design*	*Eligibility criteria*	*Sample size Gender Median age (range) dropout patients**	*Temsirolimus administration*	*Concomitant therapy (Chemotherapy/ radiation)*	*Response assessment*	*Response rate*	*Survival and TTP*
Wick et al[16]	Phase II study	–Newly diagnosed glioblastoma without MGMT promoter hypermethylation –Patient status: NA	Temsirolimus arm; N=56 M=62.5%, f=37.5% 54.9 y (28.2-74.7) dropout N=0	–25 mg –IV infusion weekly (beginning at day -7 from the RT, continued until progression)	Temsirolimus arm; Fractionated focal irradiation at a dose of 2 Gy per fraction given once daily five days per week (Monday through Friday) over a period of six weeks, for a total dose of 60 Gy	MacDonald criteria	CR=NA PR=NA SD=NA	PFS; 5.4 PFS6; NA OS; 14.8
			Temozolomide arm; N=55 M=65.5%, f=34.5% 57.7 y (24.4-76.0) dropout N=0	No temsirolimus	Standard RT/TMZ→TMZ		CR=NA PR=NA SD=NA	PFS; 6 mos PFS6; NA OS; 16 mos
Piha-Paul et al[24]	Phase I, open-label, dose-escalation clinical trial	Advanced or metastatic solid tumors -refractory to standard therapy or for which no standard therapy was available.	6 CNS tumor (2GBM) M=NA, f=NA% 6 y (3-14) dropout N=0	–25 mg –IV infusion weekly –3-weeks cycle	Chemotherapy; –Bevacizumab –5 or 10 mg/kg on day 1. No RT	Modified MacDonald criteria	CR=0 PR=1 SD=1	PFS=NA PFS6=NA OS=NA TTP=3.7 mos
Wen et al[21]	Phase I study	–Supratentorial high-grade gliomas –Tumor recurrence –≥12 w from completion of radiotherapy –Phase I; no limitation of prior therapies –Adults –KPS ≥60, –Estimated Survival ≥8 weeks, –Patients on EIAEDs or with medical history of m-TOR inhibitor or EGFR inhibitor were excluded	N=9 M=55%, f=45% 57 y (33-74) dropout N=3	–50 mg –IV infusion weekly –Escalate toward dose of 170 mg/week	Chemotherapy; –Erlotinib –150 mg/day –Oral on an empty stomach No RT	MacDonald criteria	CR=0 PR=0 SD=2	Some were involved in phase II but not specified

TABLE 1 *(continued).* Study characteristics and outcomes.

Reference	*Study design*	*Eligibility criteria*	*Sample size Gender Median age (range) dropout patients**	*Temsirolimus administration*	*Concomitant therapy (Chemotherapy/ radiation)*	*Response assessment*	*Response rate*	*Survival and TTP*
Wen et al[21] *(continued)*	Phase II study#	Equal to phase I except in Phase II; 1. Required tumor tissue from prior surgery 2. Received treatment for no more than 2 prior relapses 3. Up to 12 patients to receive treatment with both study drugs prior to surgery	Chemotherapy; N=43 M=72%, f=28% 50 y (20-69) dropout N=1	MTD (15 mg weekly) based on the first 4 weeks of treatment	Chemotherapy; –erlotinib -150 mg/day (4-weeks) –Escalate toward dose of 175 mg /day (2weeks)		Chemo therapy; CR=0 PR=0 SD=12	PFS=2 mos PFS6=13% OS=NA
Lassen et al[23]	Phase II Trial Open label	–Recurrent GBM –Previous treatment with bevacizumab –≥4 w from last chemo-therapy (≥ 6 w if nitro-sourea or mitomycin C) –≥18 years old Performance status (PS) 0-1;	N=13 M=38%, f=62% 48 y (24-72) dropout N =3	–25 mg –IV infusion weekly –4-weeks cycle	Chemotherapy; –Bevacizumab –10 mg/kg –30-90 minutes IV infusion days 8 and 22 No RT	RANO criteria	CR=0 PR=0 SD=2	PFS=2 mos PFS6=NA OS=3.7 mos TTP=NA
Lee et al[28]	Phase I study	–GBM –Unequivocal tumor recurrence gliosarcoma –No previous treatment with bevacizumab –Progression after radiotherapy –≥42 d from completion of radiotherapy –Phase I; any number of prior relapses –≥18 years old –KPS ≥ 60 –Estimated survival ≥8 weeks –Patients on EIAEDs were excluded	N=13 M=69%, f=31% 50 y (32-59) dropout N=0	–25 mg –IV infusion weekly –Increased by 25 mg/week (if well tolerated)	Chemotherapy; –Sorafenib –400 mg daily –Escalate toward dose of 800 mg daily No RT	MacDonald criteria	Some were involved in phase II but not specified	Some were involved in phase II but not specified

TABLE 1 *(continued).* Study characteristics and outcomes.

Reference	*Study design*	*Eligibility criteria*	*Sample size Gender Median age (range) dropout patients**	*Temsirolimus administration*	*Concomitant therapy (Chemotherapy/ radiation)*	*Response assessment*	*Response rate*	*Survival and TTP*
Lee et al[28] *(continued)*	Phase II study	Equal to phase I except –Phase II; received treatment for no more than 2 prior relapses	N=18 M=50%, f=50% 50 y (24-64) dropout N=0	MTD based on phase I; –25 mg –IV infusion weekly	MTD based on phase I; –Sorafenib –400 mg bid No RT		CR=0 PR=2 SD=NA	PFS=2 mos PFS6=0% OS=NA TTP=NA
Geoerger et al[26]	Phase II trial Open-label trial	–Refractory or relapsed high-grade glioma One -21 years old KPS ≥ 60	17 high grade glioma (GBM=3) M=65%, f=35% 12 y (1-21) dropout N =0	–75 mg/m^2 –IV infusion weekly –3-weeks cycle	No chemotherapy; No RT	RECIST criteria	CR=0 PR=0 SD=1	PFS=NA PFS6=NA OS=NA TTP=NA
Sarkaria et al[31]	Dose-escalation phase I trial	–Newly diagnosed GBM –One-6 w after biopsy or resection –≥18 years old –ECOG score 0-2	N=27 M=60%, f=40% 58 y (46-71) dropout N=2	–25 mg –IV infusion weekly –Escalate dose to 50 mg/week and 75 mg/week.	Chemotherapy; –Temozolomide During radiation; Oral 75 mg/m2/day Adjuvant (days without radiation); 200 mg/m^2 (on days 1 to 5 every 28 days for 6 cycles) RT; Total dose of 60 Gy, in 30 fractions, delivered to partial brain fields	End points Primary; MTD, Secondary; Best objective status, time to progression, changes in immune cell profile	CR=NA PR=NA SD=24	PFS=NA PFS6=NA OS=13.3 mos
Chang et al[22]	Phase II Trial	–Recurrence GBM –Prior low-grade glioma and a subsequent GBM –Relapsed after radiation therapy ≥ 4 w from last radiation therapy –Received treatment for no more than 2 prior relapses –≥18 years old. –KPS ≥ 60 –Estimated survival >8 W	N=43 M=65%, f=35% 48 y (26-71) dropout N=2	–250 mg –30 min IV infusion weekly –4-weeks cycle	No chemotherapy; No RT	Stable tumor/or smaller in size, clinically stable patient, stable/ decreased corticosteroid doses	CR=0 PR=2 SD=20	PFS=NA PFS6=2.4% OS=NA TTP=2.2 mos

TABLE 1 *(continued).* Study characteristics and outcomes.

Reference	*Study design*	*Eligibility criteria*	*Sample size Gender Median age (range) dropout patients**	*Temsirolimus administration*	*Concomitant therapy (Chemotherapy/ radiation)*	*Response assessment*	*Response rate*	*Survival and TTP*
Galanis et al[25]	Phase II Trial	–Primary or recurrence grade 4 astrocytoma –Received just one chemotherapy regimen –≥ 4 w from last chemotherapy (≥ 6 w if nitrosourea) –≥ 12 w from completion of radiotherapy –≥18 years old –ECOG score 0-2 fixed dose of corticosteroids or no corticosteroids for≥ 1 w before baseline scan	N=65 M=59%, f=41% 54 y (19-79) dropout N =1	–250 mg –IV infusion weekly –4-weeks cycle	No chemotherapy; No RT	MacDonald criteria	CR=0 PR=0 SD=0	PFS=NA PFS6=7.8% OS=4.4 mos TTP= 2.3 mos

*In consideration of patient loss in studies interval, omitted patients was declared; # one surgical arm (with only 3 patients) was defined in this phase, but since they were not providing any information, we exclude this arm. CR= Complete Response; ECOG= Eastern Cooperative Oncology Group; EGFR= Epidermal growth factor receptor; EIAEDs=enzyme-inducing antiepileptic drugs; F= Female; GBM= Glioblastoma multiforme; Gy=Gray (Radiology); IV= Intravenous; KPS= Karnofsky Performance Scale; M= Male; MTD= Maximum Tolerated Dose; MGMT= Methyl Guanine Methyl Transferase; mos= months; N= Number; NA= Not Available; OS= Overall Survival; PR= Partial Response; PFS= Progression Free Survival; PFS6= Progression Free at 6 months; RANO= Response Assessment in Neuro-Oncology Criteria; RECIST= Response Evaluation Criteria in Solid Tumors; RT= Radiotherapy; SD= Stable Disease; TMZ= temozolomide; TTP= Time To Progression; W= Week(s).

Therapy characteristics

Therapy with temsirolimus had been continued for each patient, unless disease progression and/or dose limiting toxicities (DLTs) occurred. Intravenous (IV) temsirolimus was administered weekly in all studies, and the variation in temsirolimus regimen was originated from its dosing and type of concurrent chemo/radiotherapy. Temsirolimus was used mostly (in 6 studies) in doses less than 100 mg/week (often 25 mg/week) and 250 mg/week in 2 other studies. Only one study had a different treatment plan and based on body surface area (70 mg/m^2/week).

Temsirolimus as a single agent was used only in 3 studies. In the other 5 studies, it was concurrently used with one of the following chemotherapeutic agents: bevacizumab, erlotinib, sorafenib or temozolomide (TMZ). Concurrent radiotherapy was performed in 2 studies. The concomitant chemotherapy dose and radiotherapy characteristics have been listed in Table I.

Premedication by IV antihistamine 30 min before starting the temsirolimus infusion was used in 3 studies. There is no other premedication in other studies.

Efficacy

Response to the treatment was assessed based on the Macdonald criteria or its modified version in 6 studies and one study used response evaluation criteria in solid tumors (RECIST). Two other studies did not use any specific criteria and assessed patients by their own measures. Patients finally were evaluated based on complete response (CR), partial responses (PR) and stable diseases (SD). Survival was reported as overall survival (OS), progression free at 6 months (PFS6), median progression free survival (PFS) and time to progression (TTP). Each study only reported some of these response and survival measures, which make it difficult to compare the results.

From overall 292 enrolled patients, a total of 12 patients left the studies and 280 remained. No CR was reported in studies. The longest PFS was 5.4 months, which had achieved in combination with standard RT[16]. The most percentage of PFS6 (13%) was reported by Wen et al[21] that used temsirolimus in combination with erlotinib. The efficacy parameters for each study are shown separately in Table I. There was no report of better temsirolimus efficacy (as monotherapy or in combination with other agents) compare to standard therapy outcomes (response rate or survival).

The presence of the blood-brain barrier and inadequate penetration of the agent to the infiltrative tumor cells was the one of the estimated cause for lack of efficacy[22]. Even though some studies believe that lipophilic molecular structure of temsirolimus warranted its sufficient concentration in CNS[23,24]. Some of the studies recommended that trying temsirolimus with other combination is worth to try[22,25,26].

Molecular and immune profile studies

Molecular markers were investigated in 3 studies. The main studied markers were Akt and p70s6 phosphorylation, EGFR amplification, PTEN deletion and PTEN expression. The most frequent problem in studying biomarkers was few patients with sufficient tumor samples. Some associations were found in the studies, which mostly were not statistically significant. In following we report the significant correlations. Neuroimaging response was significantly correlated to p70s6 kinase phosphorylation in baseline tumor samples in monotherapy with temsirolimus[25]. Also, in combination therapy with temsirolimus plus standard RT, phosphorylated m-TOR Ser2448 was associated with prolonged OS in newly diagnosed glioblastoma without MGMT promoter hypermethylation. Also, highly enriched p-m-TOR Ser2448 positive cases had a strong association with better treatment outcome by temsirolimus, while there were no differences in the TMZ/RT→TMZ group[16].

Pharmacokinetics study

From all 9 references, pharmacokinetics (PK) only was performed in 4 studies which were in phase I trial. The blood concentration of temsirolimus and its metabolite (sirolimus) and PK parameters were measured in these 4 studies and patients' PK profiles were compared.

Six GBM patients on EIACs were evaluated regarding the effect of enzyme-inducing antiepileptic drugs (EIACs) on PK of temsirolimus monotherapy[25]. They were compared to six RCC patients who were treated in the previously reported phase II study and they not received EIACAs[27]. They found that therapeutic levels were achieved despite the effect of EIACs on temsirolimus metabolism[25].

PK profile of temsirolimus and its metabolite, in both adolescent and pediatric patients, were assessed. Temsirolimus and sirolimus elimination showed a polyexponential and monoexponential way, respectively. Data from peak concentration (Cmax) and steady-state area under the curve

(AUC) of temsirolimus were not significantly related to the response, age, body surface area and weight. In contrast, for sirolimus, dose-related association in steady-state AUC were observed with increase of age, body surface area and weight[26].

No significant changes in PK parameters of temsirolimus, sirolimus, erlotinib or sorafenib and their metabolites were found during their concomitant use in study period[28,21]. Even in comparison with previously PK published studies of these drugs[29,30].

Safety

Toxicities were evaluated in studies based on common toxicity criteria (CTC) version 2, 3 or 4. Four toxic deaths were announced among total 292 enrolled patients. One death from disease progression in treatment interval was reported in temsirolimus monotherapy at the dose of 75 mg/m^2/week by Geoerger et al[26]. Three Infection-related toxicities, that led to death, were noted in combination therapy with temsirolimus plus standard RT/TMZ→TMZ by Sarkaria et al[31].

The most prevalent DLT was thrombocytopenia. The common dose modification was due to hematologic toxicity (i.e. ANC <1000/μL or platelets <100,000/μL) and Grades III and IV non-hematologic toxicity (Table II). In a study was found a correlation between hyper-lipidemia adverse effect and better radiologic response[25].

In general the combination of temsirolimus with other agents or standard treatment caused more adverse effect and therefor reduction in MTDs.

Grant support and conflict of interest

Two studies were sponsored by temsirolimus pharmaceutical manufacturer (Wyeth Pharmaceuticals, a subsidiary of Pfizer Inc.), 5 others were funded by academic sources and 2 articles declared no grant sources. Also 4 studies declare that their authors are employee or consultant in temsirolimus manufacturers.

DISCUSSION

In this review, we evaluated the different outcomes of temsirolimus in the treatment of GBM from included published articles. The results do not show promising effects of temsirolimus. Regarding to the last WHO report on CNS tumors in 2016, the best outcomes reported for GBM after concomitant surgery, radiotherapy and chemotherapy were 15 and 31 months of median overall survival for IDH-wild type and IDH-mutant glioblastoma, respectively[32,33]. Current study, which specifically included temsirolimus researches, likewise failed to achieve better than WHO reported outcomes.

Signal transduction in malignant cell can affect its apoptosis and survival. There are three major signaling pathways including: (i) the phosphatidylinositol 3-kinase (PI3K)/AKT kinase cascade; (ii) the protein kinase C (PKC) family; (iii) the mitogen-activated protein kinase (MAPK) signaling cascades[34]. Temsirolimus blokes m-TOR as a major downstream of PI3K but cannot interfere with other pathways. The effectiveness of m-TOR inhibitors has been shown in preclinical studies. Loss of PTEN function via gene mutation, deletion or promoter methylation has been reported in RCC and glioblastoma[34,35]. Temsirolimus has been approved in RCC[17] and based on the mutual trait between RCC and GBM; the temsirolimus efficacy in GBM also has been questionable[34,35].

We discussed different aspects of all the 9 references based on treatment characteristics; temsirolimus as single agent or separated different concomitant therapies with temsirolimus. Focus of discussion is on outcomes and adverse effects. The prognostic factors for GBM patients like age, performance, gender, newly diagnosed or tumor recurrence, were not discussed in the studies. Of course some of the studies focus on molecular alteration as a prognostic factor, as we noted below.

Temsirolimus as single agent

Three studies used temsirolimus as a single agent for GBM treatment. The dose of temsirolimus in 2 studies was a flat dose of 250 mg/week, which is 10 folds of temsirolimus approved dose in RCC; nevertheless, the treatment was well tolerated[22,25]. In Chang et al[22] and Galanis et al[25] findings, common criteria for response was PFS6 that occurred respectively in 2.3% and 7.8% of adults with recurrent glioblastoma. Both studies could not reach to the treatment goal as defined by 15% and 10% PFS6, respectively. Galanis et al[25] reported 36% of patients had improvement in neuroimaging (with fixed or reduced steroid doses), that indicate promising perspective in future studies. In this study Cmax of temsirolimus for patient on EIAEDs were reduced; however, it was in therapeutic range. This cannot be generalized to studies with dose of 25 mg/week with EIAEDs utilization, because their levels may have fallen below the therapeutic range.

TABLE 2. Evaluation of safety.

Reference	Treatment	Toxicity	Grade III (%)*	Grade IV (%)	Other details	Dose modifications guideline; (patients undergo dose reduction)
Wick** et al[16]	Temsirolimus +RT	Temsirolimus arm; Lymphocytopenia Neutropenia	 16.4 1.9	 — 1.8	—	Due to hematological toxicity, non-hematological toxicity in temsirolimus arm; Dose reduction (19.1%) Discard of therapy at least during one cycle (68%) Hold of therapy (58%)
Piha-Paul et al[24]	Temsirolimus + bevacizumab	Anorexia Weight loss Nausea Thrombocytopenia Liver function test abnormality	17 17 17 17 17	— — — — —	—	Hold of therapy for two weeks (33% of high grade glioma patients) because of; –Grade 3 anorexia, nausea and weight loss; and thrombocytopenia and ALT elevation, In both cases, treatment was stopped following disease progression
Wen et al[21]	Temsirolimus + erlotinib	Phase I; Rash Thrombocytopenia Cardiac ischemia Dehydration Diarrhea Hypophosphatemia Elevated triglyceride Infection Liver function test abnormality Mucositis Phase II; Rash Mucositis Hypophosphatemia Lymphopenia Thrombocytopenia Fatigue Dry skin Elevated cholesterol Elevated triglyceride Hyperglycemia Hypocalcaemia Hyponatremia Liver function test elevation Pain in limb Weakness	 44 11 — 11 11 11 11 11 11 11 23 11 20 20 4.6 4.6 2.3 2.3 2.3 2.3 2.3 2.3 2.3 2.3 2.3	 — 11 11 — — — — — — — — — — — 2.3 0 0 0 2.3 0 0 0 0 2.3 0	–Grade 1 or 2 diarrhea (44%), mucositis (29%), and rash (58%) were the most common adverse events	Dose reduction because of; –Grades III thrombocytopenia –Grades IV anemia and neutropenia, –Grades III–IV non-hematologic toxicity Discard of therapy (11% of patients) because of toxicity.
Lassen et al[23]	Bevacizumab + temsirolimus	Elevated cholesterol Elevated triglyceride Thrombocytopenia Infection Hypertension Hyperglycemia Deep-vein thrombosis	40 10 10 10 10 10 10	— — — — — — —	–One grade 2 hypersensitivity reaction	Discard of therapy because of; –DLT > 2/10 patients –Any serious adverse events not described in the summary of product characteristics (SPC) –PR not observed in at least 1/10 patients (RANO criteria) Because of third condition trial was terminated early

TABLE 2 *(continued)*. Evaluation of safety.

Reference	*Treatment*	*Toxicity*	*Grade III (%)**	*Grade IV (%)*	*Other details*	*Dose modifications guideline; (patients undergo dose reduction)*
Lee et al[28]	Sorafenib + temsirolimus	Sorafenib 200 mg bid + temsirolimus 25 mg IV weekly; Elevated cholesterol Elevated triglyceride Lymphopenia Hypophosphatemia Liver function test abnormality Sorafenib 400 mg bid + temsirolimus 25 mg IV weekly; Elevated cholesterol Thrombocytopenia Lymphopenia Hypophosphatemia Hemorrhoids	 8 8 8 8 8 5 5 5 5 5	 — — — — — — — — — —	—	Dosage Level 0 Dose reduction because of; –Grade 4 hematologic toxicity; –Grade 3 thrombocytopenia lasting more than 7 days –Grade ≥3 nonhematologic toxicity –Any intolerable grade 2 nonhematological toxicity –Grade ≥3 hematological toxicity requiring dose reduction during the first 28 days of treatment –Any toxicity resulting in treatment delay greater than 1 week during the first 28 days of treatment Dosage Level 1 Dose reduction (11.1 % of high grade glioma patients) because of; grade 3 lipase and grade 3 rash and pruritus
Geoerger et al[26]	Temsirolimus	Thrombocytopenia Anemia Liver function test Abnormality Neutropenia Infection Dyspnea Hypoxia Hyperlipidemia Hypophosphatemia	17 8 8 6 4 4 4 4 4	— — — — — — — — —	–Thrombocytopenia was the predominant DLTs –One toxic death	Hold of therapy and dose reduction (12% of high grade glioma patients) because of; –Hematologic toxicity ANC <1000/μL or platelets <75,000/μL –Grades III-IV non-hematologic toxicity
Sarkaria et al[31]	Temsirolimus + RT + TMZ	Elevated cholesterol Elevated triglyceride Thrombosis Dyspnea related to Pulmonary embolus	3.7 3.7 3.7 —	— — — 3.7 —	Three death from infection-related toxicities (during the window of (radiation/temozolomide/ temsirolimus)	No DLTs at dose level 0 (25 mg/week) or dose level 1 (50 mg/week) during radiation. Dose reduction at dose level 2 (75 mg/week), (33% patients) because of toxicity and continued by <75% of the planned temsirolimus doses.
Chang et al[22]	Temsirolimus	Lymphopenia Elevated cholesterol Anemia Elevated triglyceride Stomatitis	14 9 5 5 2	— — 2 7 5	No toxic death	Dose reduction because of; –Stomatitis; To 170 mg/week in many patients (34.7% of patients)
Galanis et al[25]	Temsirolimus	Elevated cholesterol Thrombocytopenia Hyperglycemia Rash Elevated triglyceride Fatigue	11 9 8 8 8 6	— — — — — —	Two grade 5 events (one pneumonia, one pneumonitis)	Hold of therapy because of; –Hematologic toxicity; ANC <1000/μL or platelets <100,000/μL –Grades III-IV non-hematologic toxicity Dose reduction (28% of patients) because of; –Grade III toxicity; 25% dose reduction –Grade 4 toxicity; 50% dose reduction

*Toxicity ratios based on total enrolled patients were reported, otherwise it has been mentioned. ** Toxicity ratios based on 53 patients. ANC= Absolute Neutrophil Count; bid= Twice a Day; DLT= Dose Limiting Toxicities; IV= Intravenous; PR= Partial Remission; RANO= Response Assessment in Neuro-Oncology Criteria.

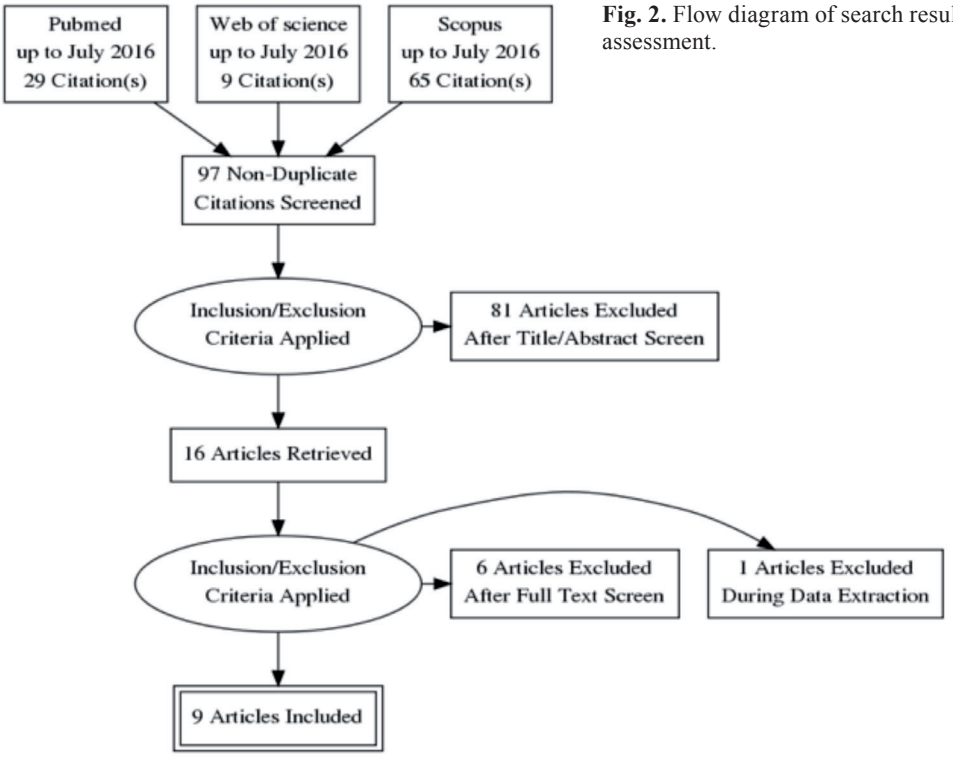

Fig. 2. Flow diagram of search results, screening and eligibility assessment.

The third study was performed by Geoerger et al[26] which administered 75 mg/m^2/week that is approximately 5 folds of standard flat dose of 25 mg/week of temsirolimus as monotherapy in pediatric patients and did not show new adverse effect compare to adults. In this study, 2 SD in 3 glioblastoma patients were observed, but like past 2 studies, no objective response was observed. Blockage of m-TOR with temsirolimus monotherapy makes it possible for the malignant cell to use escape metabolic pathways and survive[21]. Therefore, use of combination therapy can overcome this source of resistance, as it recommended by above-mentioned studies. Although the blood sample of temsirolimus and its metabolite is available for drug level evaluation, we do not know whether it is representative for drug level in tumor[22]. It has been stated that the effectiveness of temsirolimus has a potential correlation with m-TOR activity and molecule metabolisms in tumoral cell. Thus, if these mechanisms would be ignored before initiation of treatment, we may be faced with underestimated results[34,26].

Temsirolimus plus standard RT

European Organization for Research and Treatment of Cancer (EORTC) performed a randomized clinical trial in 2016[16] on newly diagnosed glioblastoma without MGMT promoter hypermethylation. Since every tumor response to treatment differently[36], pre-treatment evaluation of molecular alteration in tumors, can predict the therapy effectiveness to some extent[25]. They used temsirolimus in combination with standard RT instead of TMZ compared with standard RT/TMZ→TMZ. EORTC reported no superiority of temsirolimus to TMZ in combination with standard RT, by evaluating patients OS and PFS[37]. They suggested temozolomide can be safely substituted by temsirolimus in combination with standard RT in patients with unmethylated MGMT glioblastoma that is resistant to TMZ[38].

Infectious related toxicities are one of the complications associated with standard RT/TMZ→TMZ particularly with TMZ {Stupp, 2005 #36}[37]. This complication is associated with temsirolimus as well[39]; therefore, it can be aggravated by their combination. Based on preclinical studies that have been suggested use of this combination[40,41], Sarkaria et al[31] in 2010 studied this assumption in newly diagnosed glioblastoma patients. In this study temsirolimus was added to TMZ in the standard regimen of concurrent radiotherapy and TMZ followed by adjuvant TMZ (RT/TMZ→TMZ). The study reported that combination therapy with temsirolimus/temozolomide/radiation was associated with significant suppression of cellular, humoral and innate immunity. They could have managed the increased infection rate with antibiotic prophylaxis and by limiting the duration of temsirolimus therapy. By this combination, 24 out of 25 patients have achieved SD, which is interesting. Since toxicity

most occurred in the period of adjuvant temozolomide/temsirolimus use, they have recommended using temsirolimus only during concomitant radiation and temozolomide for limiting infection related toxicities in phase II trial[31].

Temsirolimus plus bevacizumab

Two studies used temsirolimus and bevacizumab combination in GBM patients based on promising effect of it in the prior trials. Combination of bevacizumab with other chemotherapy agents is also effective in GBM[42,43]. Bevacizumab monotherapy has been approved by FDA for glioblastoma in 2009[44]. Lassen et al[23] evaluated the combination of bevacizumab and temsirolimus in adults, but they did not suggest this combination in the treatment of GBM for further studies. Their study terminated earlier because in 1/10 patients PR did not occur. Although they have 2 SD for 4 months between 10 enrolled patients. The second study, which was performed by Piha-Paul et al[24], had better results with temsirolimus plus bevacizumab. They had 2 pediatric patients with GBM between 6 cases with refractory CNS tumors; one achieved PR and another had SD for 16 weeks. Both were treated with bevacizumab previously, which can affect their outcomes. Due to the small sample size, the authors suggested repeating this treatment plan in larger studies[24]. Adverse effects in both studies were mild and therapy was well tolerated[24,23].

Temsirolimus plus targeted therapies

North American Brain Tumor Consortium (NABTC) in 2012 used sorafenib in combination with temsirolimus[28]. The outcomes of this combination therapy were not convincing because no PFS6 was obtained and minimal activity for recurrent GBM in both phases of the study was found. This lack of efficacy was mostly due to DLTs (mostly thrombocytopenia) that caused temsirolimus dose adjustment, therefore maximum tolerated dose (MTD) reduced to 25 mg/ week (one-tenth of monotherapy dose). Other reasons for lack of efficacy can be listed as follows: (i) impermeability of blood brain barrier to sorafenib {Agarwal, 2011 #43}[19]; (ii) alternative metabolic pathway like MAPK that has not been significantly inhibited by sorafenib[45]; (iii) loss of feedback inhibition and paradoxical Akt activation because of m-TOR inhibition by sirolimus[46,47], which also can occur by temsirolimus as an rapamycin analogue.

NABTC also conducted the study in 2014 with combination therapy of erlotinib and temsirolimus in GBM[21]. It has been stated that glioblastoma with EGFRVIII and wild type PTEN and tumors with low levels of phospho-Akt can be sensitive to EGFR inhibitors[48,49], and it is suggested that using m-TOR inhibitors in combination with EGFR inhibitors can enhance efficacy[50]. This combination also failed to show efficacy, like other combinations. This failure is probably due to same reasons as sorafenib and temsirolimus combination i.e. DLTs, which led to reduction of MTD of temsirolimus to 15 mg/ week. Redundant signaling pathway has been suggested as a possible cause for lack of efficacy[51,52]. Drug levels for both erlotinib and temsirolimus in tumoral tissue after resection surgery compered to plasma levels in 3 patients shown poor CNS penetration[21]. Like sorafenib, there is no interaction between temsirolimus and erlotinib.

Using targeted therapy in combination with temsirolimus seemed to be theoretically rational and recommended repetitively by previous studies[28,26], but failed to show efficacy. There are few suggestions for future studies from NABTC, which were also mentioned in our included studies: (i) using an agent with lower mutual side effects; (ii) using prophylaxis pretreatment to prevent DLTs; (iii) use of combining targeted agents to inhibit overlapping pathways and/or several steps of the same signaling pathway; (iv) overcoming resistance of GBM by targeted therapies. We can overcome GBM resistance by using agents that can enhance CNS penetration of medicines and agents that inhibit the sirolimus-insensitive m-TOR complex 2 in addition to the sirolimus-sensitive m-TOR complex1. These have been proved to be effective in preclinical studies[53].

CONCLUSIONS

As a single agent and in combination with radiotherapy and/or chemotherapy, temsirolimus has shown minimal advantages compare to current standard treatment. The important result obtained through these clinical studies was introducing 2 outcome predictive biomarkers, which enhance responsiveness to temsirolimus therapy in GBM: p70s6 kinase phosphorylation and p-m-TOR (Ser2448). The temsirolimus was well tolerated in GBM patients even in pediatrics at the doses higher than approved one (flat dose of 25 mg/week), excepting when it was combined with targeted therapies. Accordingly, evidence is not supporting the use of temsirolimus in any form at this time point. Some modifications are suggested for further studies based by cited studies and literature.

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Conflict of interests
There is no conflict of interest to report.

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