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THE ROLE OF CELECOXIB IN GLIOBLASTOMA TREATMENT: A REVIEW OF LITERATURE

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Abstract – *Objective:* *Glioblastoma (GB) is the most aggressive and lethal type of brain tumor. Despite the standard treatments and improvements, the overall survival (OS) and progression free survival (PFS) are not optimal. Celecoxib (CEL) has been considered as one of the adjuvant agents in patients with GB due to its different mechanisms in recent years.*

Materials and Methods: *A systematic search was performed in EMBASE, MEDLINE, ClinicalTrials.gov, Web of Science, Google Scholar and Cochrane Central Register of the Controlled Trials databases to get access to the trials that investigated the potential benefits of CEL in the treatment regimen of patients with GB.*

Results: *From 77 studies, twelve clinical trials with 690 patients from 2004 to 2015 were included. The trials were often in phase II and temozolamide was the main agent of the treatment regimen. CEL was administered mostly at high dose of 400 mg twice daily and it was well tolerated. CEL has shown some promising effects but only in studies which patients were not eligible for standard treatment due to their age or clinical conditions.*

Conclusions: *CEL administration in tested doses is safe and practical for GBM patients. It could be considered as one of the choices in the therapeutic protocol of GB along with the main drugs commonly used in chemotherapy regimen especially in the elderly patients who are not eligible for standard treatment.*

KEYWORDS: *CEL (celecoxib), GB (glioblastoma), Brain tumor, COX-2 inhibitor, Celebrex, Glioblastoma multiforme, GBM, Grade IV astrocytoma.*

INTRODUCTION

Glioblastoma multiforme (GBM) or Glioblastoma (GB) also named grade IV astrocytoma, is the most common and lethal type of the brain tumor which originates from the glial cells. GB represents 14.9% of all primary brain tumors and 56.1% of all glioma cases[1, 2]. This tumor is extremely malignant and grows rapidly although distant metastases are rare[3]. Common clinical symptoms of the disease include headaches, seizure and memory impairment but other symptoms may also occur depending on the tumor location[4].

The current standard treatment for GB is surgical resection followed by radio-chemotherapy and adjuvant treatment. Common administered chemotherapy agent is temozolomide (TMZ), an alkylating agent that is administered concurrently within radiation and after radiation as an adjuvant treatment[5]. Although, it is found that Methyl Guanine Methyl Transferase (MGMT) gene causes resistance of tumor cells to alkylating agents and its Methylation could lead to prolonged survival rates in patients with GB[6].

Other choices for treatment of GB are also available. There are some biologic and targeted immunotherapies in GB treatment including epidermal growth factor receptor (EGFR)-targeted therapies, targeting other receptor tyrosine kinases, PI3K/AKT/mTOR and MAPK signaling pathways, DNA

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repair and cell cycle control pathways and epigenetic deregulation, tumor metabolism[7] and anti-vascular endothelial growth factor receptor (anti-VEGF) antibody like bevacizumab[8]. One more treatment for recurrent GBM is NovoTTF-100A device which interrupts tumor cells mitosis cycle as they enter anaphase stage leading to cell death[9]. There are also a number of drugs which have shown anti-neoplastic effects *in vitro*, such as antidepressants, antiepileptic drugs, statins, beta blockers and other antihypertensive agents. These could be a target for future clinical studies to improve survival in patients with GBM[10].

So far, despite the abovementioned treatments, GBM is the most common and aggressive type of brain tumor, without a certain effective therapeutic approach. Therefore, it seems necessary to carry out more comprehensive reviews of existing alternative options to promote patients' overall survival (OS) and reduce tumor progression rate.

Multiple cell and animal studies have explored the various mechanisms explaining celecoxib (CEL) effects on GB cells including; 1) increased radio-sensitivity of cancer cells through endoplasmic reticulum stress; 2) increased GB cells death in combination of CEL with bortezomib by aggravating endoplasmic reticulum stress[11]; 3) positive effects on destroying C6 rat glioma orthotropic model in combination with TMZ[12]; 4) significant improvement in radio-sensitivity of GB cells by angiogenesis inhibition[13].

In the present review, we assessed related clinical trials through a systematic search to evaluate the effect of CEL on progression free survival (PFS), OS and quality of life in patients with GBM.

MATERIALS AND METHODS

We performed a review of the literature with systematic search approach regarding CEL role in GBM malignancy. We extracted CEL efficacy and safety characteristics from selected studies in patients with GBM.

Search strategy

We carried out the search through the MEDLINE, EMBASE, ClinicalTrials.gov, Web of Science, Google Scholar and Cochrane Central Register of Controlled Trials databases up to September 2019. The included search terms were: celecoxib, Celebrex®, glioblastoma, glioblastoma multiforme, GBM, grade IV astrocytoma and brain tumor. The references of articles were also checked to discover any omitted relevant studies.

Inclusion and exclusion criteria

The inclusion criteria were English studies which were performed on adult patients (age ≥ 18 years old) with definite GB diagnosis for all enrolled patients. Studies were excluded if they were letters, conference abstracts, editorials and reviews or if the studies subjects were animal and cell cultures.

Data extraction

Data were extracted from selected studies and reported into 2 Tables. In Table 1, patients' demographic information (age, gender), study characteristics (Study design, Eligibility criteria, CEL dosage and Concomitant therapy), medication regimen efficacy parameters (Response/Safety assessment, Response rate and Survival and Time to Progression) and CEL proposed mechanism of action are reported. In Table 2, the extracted data of CEL safety (grade III and IV toxicities, dose modifications and safety information) are summarized.

RESULTS

Initially 77 studies were found. After title and abstract screening and full-text evaluation 65 studies were excluded and 12 remained. In Figure 1, flow chart of search results is shown.

Study characteristics

Twelve clinical trials were reviewed. Time span of these studies was from 2004 to 2015 and all were in English. The studies were often phase II trials.

Patients' characteristics

A total of 690 patients had participated in all the 12 trials and they were mostly males. Patients had recurrent GB in seven studies, and they were newly diagnosed with GB in other five studies. Participants were adults and in the Welzel *et al*[14] trial, they were all older than 65 years.

Almost all the patients had to have adequate bone marrow, liver and kidney function to be enrolled in the trials. The used performance scale in included trials was Karnofsky Performance Status (KPS). In most studies, KPS was more than 60%. In two studies, mean KPS was more than 80%[15, 16], and in two other studies KPS was < 70% and patients were not eligible for the standard therapy[14, 17].

TABLE 1. Study characteristics.

N.	Study	Study design	Eligibility criteria	Sample size Gender Median age (range)	CEL dosage	Concomitant therapy	Response/ Safety	Response rate assessment	Survival and TTP	CEL proposed MOA
1.	Reardon et al[18]	Phase II study	- Recurrent GBM - Adults - KPS ≥ 60% - Receiving stable corticosteroid dose 1 W prior to therapy - Adequate bone marrow, liver and kidney function	N = 37 (34 GBM, 3 AA) M = 27, F = 10 50 Y (34-68) EIAED received = 21	- 400 mg - BD	- Irinotecan; EIAED receiving; 350 mg/m^2 Not EIAED receiving; 125 mg/m^2 - W 1, 2, 4, 5 of every 6-W cycle	- MRI - CBC - Urinalysis - βHCG (in women)	CR = 3% PR = 14% SD = 35% PD = 46%	PFS; 11 W PFS6 = 25.1% OS; 31.5 W	-Enhancing anti-tumor activity of irinotecan - Reducing tumor growth by increasing apoptosis
2.	Levin et al[16]	Phase II study	- Recurrent GBM - Adults - KPS ≥ 60% - Adequate bone marrow, liver and kidney function	N = 25 M = 16, F = 9 55 Y (31-72)	- 400 mg - BD - 21 days followed by 7 days without treatment	- Accutane; 100 mg/m^2 - Daily - 21 days followed by 7 days without treatment	- MRI - Neurologic - Lab tests	PR = 0 SD = 44%	PFS = 8 W PFS6 = 19%	-Further suppression of COX-2 expression - Anti-proliferative effects
3.	Kesari et al[23]	Phase II study	- Recurrent GBM - Adults - KPS ≥ 60% - Adequate hematological function	N = 48 (28 GBM) M = 33, F = 15 53 Y (33-74)	- 200 mg - BD - 400 mg BD (> 50 kg)	- Etoposide; 35 mg/m^2, 21 days -Cyclophosphamide; 2 mg/kg, 21 days - Thalidomide; 50-200 mg daily Through 6-W cycles	- MRI - Axial and coronal T1 pre and post gadolinium images - CBC - Urinalysis - Angiogenic peptide measurement	PR = 2% MR = 9% SD = 59% PD = 30%	PFS = 11 W PFS6 = 9% OS = 21 W	- Anti-angiogenesis and anti-proliferative effects
4.	Kesari et al[24]	Phase II study	- Newly diagnosed GBM - Adults - KPS ≥ 60% - Adequate bone marrow, liver and kidney function	N = 50 M = 32, F = 18 54 Y (29-78)	- 200 mg - BD - Max dose = 400 mg BD	- TMZ; 150 mg/m^2, daily, 5 days of 28-day cycle - Thalidomide; 200 mg, daily, max dose = 1200 mg, daily	- MRI - Axial and coronal T1 pre and post gadolinium images - MGMT status - Angiogenic peptide measurement	CR = 0 PR = 11% MR = 9% SD = 47% PD = 34%	PFS = 5.9 months PFS6 = 63% OS = 12.6 months 1-Y OS = 47%	- Anti-angiogenesis and anti-proliferative effects

Continued

TABLE 1 *(CONTINUED).* Study characteristics.

N.	Study	Study design	Eligibility criteria	Sample size Gender Median age (range)	CEL dosage	Concomitant therapy	Response/ Safety	Response rate assessment	Survival and TTP	CEL proposed MOA
5.	Grossman et al[21]	Phase I study	- Newly diagnosed GBM - Adults - KPS ≥ 60% - Adequate bone marrow, liver and kidney function	N = 35 Received EIASD 22; M = 14; F = 8 Not received EIASD 13; M = 7; F = 6 - 10 patients withdraw	- 400 mg - BD	RT; 6000 cGy in 30 fractions	- MRI	NA	OS = 12 months 89% died	- Anti-angiogenesis - Inducing apoptosis - Synergistic cytostatic and/or cytotoxic effects with RT
6.	Stock hammer et al[15]	Phase II study	- Recurrent GBM - Adults - Mean KPS = 80%	N = 28 M = 20, F = 8 56 Y (27-76) - 19/28 patients with surgical resection	- 200 mg - QID	TMZ; 10 mg/m^2, BD	MacDonald criteria	NA	PFS = 4.2 months OS = 16.8 months PFS6 = 43% OS6 = 86%	- Enhancing anti-angiogenic activity
7.	Walbert et al[22]	Open-label, non-comparative study	- Recurrent GBM - Adults - Prior Ch.T, RT or both - KPS ≥ 60% - Adequate bone marrow, liver and kidney function	N = 43 M = 27, F = 16 53 Y (26-76)	- 400 mg - BD - 14 days in 28-day cycles	- Arm 1; 28-day cycles; 6-TG; 80 mg/m^2, QID, 12 doses; TMZ; 150 mg/m^2, 5 days; capecitabine; 825 mg/m^2, BD, 14 days - Arm 2; 42-day cycles; 6-TG; 80 mg/m2, QID, 12 doses, CCNU; 100 mg/m^2, one day; capecitabine; 825 mg/m^2, BD, 14 days	MacDonald criteria	CR = 2% PR = 9% SD = 33% PD = 56%	PFS6 = 14% PFS9 = 9% PFS12 = 5% OS = 32 W	- Inducing apoptosis - Augmenting Ch.T cytotoxicity - Anti-angiogenic activity - Impairing cell migration
8.	Gilbert et al[19]	Phase I study	- Newly diagnosed GBM - ≥ 10 Y old - KPS ≥ 60% - Adequate bone marrow, liver and kidney function - Without other cancer	N = 54 M = 32, F = 22 52 Y (18-76) 12 exclude at first	- Arm 6, 7, 8; 400 mg, BD	- Arm 6; TMZ, thalidomide - Arm 7; TMZ, isotretinoin - Arm 8; TMZ, isotretinoin, thalidomide	MacDonald criteria	NA	OS = 20 months 2- Y Survival = 40%	- Cytostatic and potentially cytotoxic effects - Synergistic cytostatic and/or cytotoxic effects with TMZ

Continued

TABLE 1 *(CONTINUED)*. Study characteristics.

N.	Study	Study design	Eligibility criteria	Sample size Gender Median age (range)	CEL dosage	Concomitant therapy	Response/ Safety	Response rate assessment	Survival and TTP	CEL proposed MOA
9.	Marta Penas-Prado et al[20]	Phase II study	- Newly diagnosed GBM - Adults - KPS ≥ 60% - Adequate bone marrow, liver and kidney function	N = 178 M = 123, F = 55 53 Y (18-84)	- 400 mg - BD	- 8 arms - 28- day cycles - TMZ; 150 mg/m^2, daily - Thalidomide; 400 mg, daily - Isotretinoin; 40 mg/m^2, BD	MacDonald criteria	NA	PFS = 11.6 months PFS6 = 73%	- Cytostatic and potentially cytotoxic effects - Synergistic cytostatic and/or cytotoxic effects with TMZ
10.	Welzel et al[14]	Retrospe-ctive study	- Newly diagnosed GBM - ≥ 65 Y old - Not eligible for Ch.T - Underwent RT on average 3 W after resection or biopsy	N = 146 M = 68, F = 78 74 Y (65-94)	- 200 mg - Daily - In group 3	- Group 1; EBRT - Group 2; EBRT, TMZ; 50 mg/m^2, 5 days a W - Group 3; EBRT, TMZ; 40 mg/day	- MGMT status - MRI - CBC - Medical examination	NA	PFS (months) = group 1; 3.3, group 2; 5, group 3; 4.3 OS (months) = group 1; 4.2, group 2; 10.8, group 3; 8.5	- Anti-angiogenic activity - Impairing tumor micro-milieu and/or micro-vasculature
11.	Wong et al[9]	Prelimi-nary obser-vation	- Recurrent GBM - NovoTTF used for all	N = 37 M = 23, F = 14 57 Y (30-77) in group 1, 56 Y (51-56) in group 2	- 400 mg - BD - In group 2	42- day cycles; - Group 1; Novo + bevacizumab; 10 mg/kg, every 2 W - Group 2; Novo + bevacizumab + TCCC (6- TG, 80 mg/m^2, QID, CCNU; 100 mg/m^2, one day, capecitabine; 825 mg/m^2, BD)	RANO criteria	- Group 1; SD as best response - Group 2; OR = 33% SD = 67%	PFS (months) = group 1; 2.8, group 2; 8.1 OS (months) = group 1; 4.1, group 2; 10.3	- Inhibitory effect on PG E2 production helping to reverse tumor-induced immunosuppression - Augmentation of endoplasmic reticulum stress responses induced by Novo
12.	Kersch-baumer et al[17]	Retrospe-ctive investi-gation	- GBM - KPS < 70%: not eligible for standard treatment - Post-operative	N = 9 (8 GBM, 1 AA) M = 2, F = 7 69 Y (53-85)	- 200 mg - Daily	TMZ; 20 mg, BD	MacDonald criteria	NA	TTP = 7 months OS = 9 months	-Anti-angiogenic potency by down-regulation of angiogenic growth factor and VEGF that cause blocking of endothelial cell proliferation and induction of apoptosis

GBM = Glioblastoma Multiforme; AA = Anaplastic Astrocytoma; AG = Anaplastic glioma; Y = Year(s); W = Weeks; M = Male; F = Female; NA = Not Available; N. = Number; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; CR = Complete Response; MR = Minor Response; OR = Overall Response; PFS = Progression Free Survival; OS = Overall Survival; TTP = Time To Progression; PFS6 = 6-month PFS; OS6 = 6-month OS; BD = Twice daily; QID = Four times a day; KPS = Karnofsky Performance Status; CEL = Celecoxib; TMZ = Temozolomide; EIAED = Enzyme Inducing Anti-Epileptic Drugs; RT = Radio Therapy; Ch.T = Chemotherapy; EBRT = External Beam Radiation Therapy; EIASD = Enzyme-Inducing Anti-Seizure Drugs; RANO = Response Assessment Neuro-Oncology Criteria; MGMT = Methyl Guanine Methyl Transferase; PG E2 = prostaglandin E2; VEGF = vascular endothelial growth factor; MOA = Mechanism of Action.

TABLE 2. Evaluation of safety.

N.	Reference	Treatment (all + CEL)	ADEs	Grade 3 (number)		Grade 4 (number)		Treatment modifications
				No EIAED	On EIAED	No EIAED	On EIAED	
1.	Reardon et al[18]	Irinotecan	Diarrhea	3	4	0	0	Dose reduction of irinotecan by 20% for any nonhematologic toxicity ≥ grade 3 or grade 4 hematologic toxicity
			Hyponatremia	1	0	1	0	
			Infection	1	0	0	1	
			Thrombosis	0	1	0	1	
			Anemia	1	0	0	0	
			Neutropenia	3	0	1	0	
			Thrombocytopenia	3	0	0	0	
2.	Levin et al[16]	13-cis-retinoic acid	Unremarkable	NA		NA		NA
3.	Kesari et al[23]	Etoposide + cyclophosphamide + thalidomide	Anemia	1		0		- Dose reduction of etoposide due to grade 3 and grade 4 hematological toxicities - DC in 12%
			Ataxia	1		0		
			Colitis	0		2		
			Constipation	3		2		
			Dizziness	1		0		
			Dysphagia	1		0		
			Fatigue	1		0		
			Hepatotoxicity	2		0		
			Hyperglycemia	2		0		
			Hypoxia	1		0		
			Infection	4		0		
			Leukopenia	7		6		
			Lymphopenia	9		0		
			Nausea vomiting	4		0		
			Neutropenia	2		8		
			Rash	1		0		
			Somnolence	1		0		
			Thrombocytopenia	1		0		
			Thrombosis	1		4		
			Tremor	1		0		

Continued

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

N.	*Reference*	*Treatment (all + CEL)*	*ADEs*	*Grade 3 (number)*	*Grade 4 (number)*	*Treatment modifications*
4.	Kesari et al[24]	TMZ+ thalidomide	Agitation	2	0	DC in 12% due to symptoms probably related to protocol
			Colitis	0	1	
			Constipation	6	0	
			Dizziness	1	0	
			Dyspnea	1	0	
			Fatigue	2	1	
			Hypotension	1	0	
			Infection	1	1	
			Irregular menses	1	0	
			Leukopenia	8	2	
			Lymphopenia	2	0	
			Memory loss	1	0	
			Nausea vomiting	1	0	
			Neutropenia	9	2	
			Ototoxicity	1	0	
			Rash	1	0	
			Seizure	2	0	
			Somnolence	0	1	
			Thrombocytopenia	2	3	
			Thrombosis	2	2	
			Tremor	1	0	
			Blurred vision	1	0	
5.	Grossman et al[21]	RT	- Creatinine clearance ≤ 60 mL/min	1	–	Dose reduction due to creatinine clearance = 59 mL/min
			- Gastrointestinal bleeding	1	0	
6.	Stockhammer et al[15]	TMZ	Lymphopenia	1	0	- Cotrimoxazole added as a PCP-prophylaxis - CEL DC in one patient because of allergy

Continued

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

N.	*Reference*	*Treatment (all + CEL)*	*ADEs*	*Grade 3 (number)*		*Grade 4 (number)*		*Treatment modifications*
7.	Walbert et al[22]	6-thioguanine, capecitabine, TMZ, lomustine		Lomustine	TMZ	Lomustine	TMZ	- TMZ arm; TMZ and capecitabine dose reduction due to neutropenia, capecitabine and CEL dose reduction due to gastro-intestinal symptoms - Lomustine arm; lomustine dose reduction due to hematological toxicities - DC in 4 patients (one from arm 1, 3 from arm 2)
			Anemia	5	1	–	–	
			Neutropenia	9	3	8	1	
			Leukopenia	18	3	4	0	
			Lymphopenia	15	3	5	2	
			Thrombocytopenia	8	1	1	1	
			Seizure	1	–	–	–	
			Mental status	1	–	–	–	
			Muscle weakness	1	–	–	–	
			Neuropathy	1	–	–	–	
			Alanine transaminase	1	–	–	–	
			Hypoalbuminemia	1	–	–	–	
			Hypokalemia	–	2	–	–	
			Hyponatremia	2	–	–	–	
			Hypophosphatemia	–	–	1	–	
			Anorexia	1	–	–	–	
			Colitis	–	–	1	–	
			Constipation	–	–	1	–	
			Dehydration	1	–	–	–	
			Diarrhea	2	1	–	–	
			Pain	1	–	–	–	
			Vomiting	3	–	–	–	
			Pneumonitis	1	–	–	–	
			Dyspnea	1	–	1	–	
			Fatigue	8	–	1	–	
			Sepsis	1	–	–	–	
			Thrombosis	–	–	1	–	
8.	Gilbert et al[19]	TMZ, thalidomide, isotretinoin	Lymphopenia	23		8		DC in10 patients (24%) due to toxicities
			Leukopenia	16		1		
			Thrombocytopenia	4		1		
			Neutropenia	9		4		
			Fatigue	10		0		
			DC because of ADEs	10				

Continued

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

N.	*Reference*	*Treatment (all + CEL)*	*ADEs*	*Grade 3 (number)*		*Grade 4 (number)*		*Treatment modifications*
9.	Marta Penas-Prado et al[20]	TMZ, isotretinoin, thalidomide	NA	NA		NA		NA
10.	Welzel et al[14]	EBRT, TMZ		Group 1	Group 2	Group 1	Group 2	
			Anemia	1	0	–	–	NA
			Leukopenia	2	0	1	0	
			Leukocytosis	0	0	–	–	
			Thrombocytopenia	3	0	0	0	
			Serum creatinine increase	0	0	0	0	
11.	Wong et al[9]	NovoTTF-100A, bevacizumab, 6-thioguanine, lomustine, capecitabine	NA	NA		NA		NA
12.	Kerschbaumer et al[17]	TMZ	No hematological, cardiac, gastrointestinal toxicity. No infection, fatigue, nausea, vomiting	NA		NA		NA

CEL = Celecoxib; TMZ = Temozolomide; EIAED = Enzyme Inducing Anti-Epileptic Drugs; RT = Radio Therapy; EBRT = External Beam Radiation Therapy; NA = Not Available; N. = Number; DC = Discontinue; ADEs = Adverse Drug Events; PCP = Pneumocystis Pneumonia

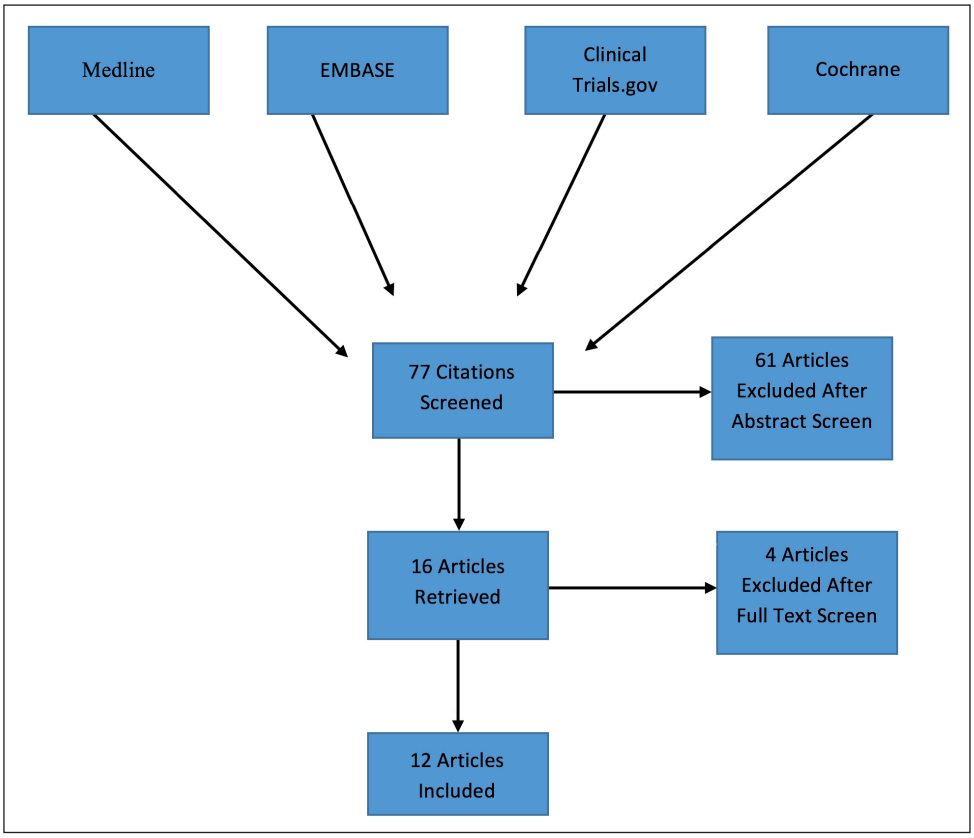

Fig. 1. Flow diagram of search results

Proposed mechanism of action for CEL

The reasons of including CEL in GBM treatment regimens can be summarized as follow: 1) showing synergistic cytostatic or cytotoxic or both effects in combination with other agents including irinotecan[18], isotretinoin[16], TMZ[14,19,20] and radiotherapy[21]; 2) reducing tumor growth through increasing apoptosis[18,21,22], 3) anti-angiogenesis and anti-proliferative properties[14-17, 21-24]; 4) impairing cell migration[22]; 5) impairing tumor micromilieu and/or microvasculature[14]; 6) inhibitory effect on PG-E2 production helping to reverse tumor-induced immunosuppression[9]; 7) augmentation of endoplasmic reticulum stress responses induced by NovoTTF-100A[9].

Treatment characteristics

In all trials, CEL was administered as an adjunctive therapy. In six studies, TMZ was the main agent of treatment regimen. In the study by Welzel *et al*[14] low-dose TMZ and CEL were used during and after External Beam Radiation Therapy (EBRT).

In four studies, other chemotherapy agents were also administered with TMZ such as thalidomide[24], 6-thioguanine plus capecitabine[22] and isotretinoin plus thalidomide[19,20]. In four studies, drugs of choice were other than TMZ in treatment including irinotecan[18], 13-cis-retinoic acid[16], etoposide, cyclophosphamide and thalidomide[23], NovoTTF-100A and bevacizumab[9]. In the study by Grossman *et al*[21], only radiotherapy (RT) was done as the main treatment option along with CEL. CEL was mostly administered at high dose of 400 mg BD (in nine trials) and in the remaining studies, CEL dose was 200 mg BD or daily.

Treatment Efficacy

Response to treatment was assessed according to the McDonald Criteria in five trials[15,17,19,20,22] and RANO Criteria only used in one trial[9]. In the remaining, response assessment was based on study self-modified measurements.

Patients' responses to treatment were evaluated by complete response (CR), partial response (PR) and stable disease (SD). Survival was reported as OS, 6-month progression free survival (PFS6) and median PFS.

Some studies did not specify any response rate[14,15,17,19-21]. Moreover, each trial evaluated these parameters differently; therefore, it was difficult to

compare the results. CR only was reported in two studies; one CEL plus 6-thioguanine and capecitabine (CR: 2%)[22], and the other one CEL plus irinotecan (CR: 3%)[18]. The highest reported percentage of PFS6 was 63% in Kesari *et al*[24] study which was a phase II study of TMZ, thalidomide and CEL for patients with newly diagnosed GB[24]. The longest reported OS was in Marta Penas- Prado *et al*[20] study (21.2 months) which was found in TMZ alone arm[20].

In some studies, there was no improvement in PFS, OS or other measurements following adding CEL to the treatment regimen.

Safety

In most studies, treatment regimens were well tolerated. A limited number of patients became toxic in grade three and four.

In Reardon *et al*[18] study (irinotecan plus CEL), grade three or four hematologic toxicities occurred in number of patients not receiving enzyme-inducing anti-seizure drugs (EIASD) and also grade four or five toxicities occurred in patients receiving EIASD[18].

In another study (13-cis-retinoic acid plus CEL), treatment was stopped in 12% of patients because of toxicities probably related to the regimen[16].

CEL dose was reduced as a result of impaired creatinine clearance in RT plus CEL trial[21] and gastrointestinal symptoms in 6-thioguanine and capecitabine plus CEL trial[22]. In one trial, CEL was stopped because of allergy in one patient[15]. More information about the grade three and four toxicities is summarized in Table 2.

DISCUSSION

The standard treatment of GB considers surgical resection followed by radiotherapy and chemotherapy. The median OS of the patients with GBM was evaluated 12 to 16 months. Despite the advances achieved in the treatment approaches during recent years, the survival time of the patients is not even close to ideal[10, 25]. Here, we reviewed the different outcomes of CEL in the treatment of GBM according to included relevant published articles.

In the present study, clinical trials in which CEL was added to the main regimen were included. Although there are various mechanisms with promising prospects for CEL efficacy, no significant results were achieved, except in studies which patients were not eligible for standard treatment. In the following, treatment characteristics studies which used CEL as an adjuvant agent are reviewed, with more emphasis on outcomes and adverse effects.

Low-dose metronomic CEL plus TMZ

Kerschbaumer *et al*[17], Welzel *et al*[14] and Stockhammer *et al*[15] studied the effect of low-dose metronomic CEL and TMZ in the treatment of GBM. It is assumed that CEL has synergistic cytostatic or cytotoxic or both effects with TMZ and the results seemed to be effective in all the three studies.

In Kerschbaumer *et al*[17] study (2015), patients who had lower KPS, combination of CEL and TMZ resulted in better quality of life and prolonged survival with no additional adverse effects. They observed that this dual anti-angiogenic low-dose metronomic chemotherapy was well tolerated by patients with poor general conditions.

In the retrospective trial conducted among elderly patients by Welzel *et al*[14] (2015), the application of low dose metronomic TMZ with CEL was equieffective compared with standard TZM radio-chemotherapy; however, the study population was not completely randomized in the treatment arms and patients in the group low-dose TMZ/CEL were older and had lower KPS with more comorbidities. Even in these circumstances, there were no significant differences in PFS and OS. Toxicity assessments were performed only 6 months after diagnosis which was not enough for detecting all aspects of toxicity. In summary, this regimen was efficient in elderly patients with significant comorbidities[14].

In study by Stockhammer *et al*[15] *(*2010), low-dose metronomic TMZ in combination with CEL after standard treatment seemed to have been effective without related toxicity in patients with recurrent GBM[15].

CEL plus NovoTTF-100A

Wong *et al*[9] showed that the combination of NovoTTF-100A and bevacizumab with 6-thioguanine, lomustine, capecitabine, and CEL could be effective in patients with end-stage recurrent GBM. The role of CEL in this regimen is augmentation of endoplasmic reticulum stress responses induced by NovoTTF-100A[9, 26]. Only three patients were treated with this regimen experiencing a prolonged median of OS and PFS which considered comparable to the outcome measures in patients under treatment with NovoTTF-100A and bevacizumab only. Although this sample size is too small to make a recommendation, the findings are remarkable and promising for the future clinical studies[9]. The patients received NovoTTF-100A and bevacizumab had a comparable PFS to the former clinical trial subjects only treated with NovoTTF-100A; however, all of the patients in the mentioned trial had better baseline clinical characteristics[9, 27].

CEL plus RT

In the clinical trial conducted by Grossman *et al*[21], patients were treated with radiotherapy only and CEL as an adjunctive therapy. CEL could have synergistic effects with radiotherapy. The median OS is not significantly different from what is expected with radiotherapy alone. It is noteworthy that patients in the group without an EIASD had a higher median of OS. This finding could be due to smaller sample size on this arm[21] or possible negative impact of phenytoin on the survival[21, 28] or maybe another metabolite of CEL should be measured to compare two arms of this study correctly[21]. The fact is that this study discontinued after introducing TMZ as an effective concomitant and adjuvant therapy with radiation due to ethical issues[21].

CEL plus other cytostatic agents

Levin *et al*[16], Reardon *et al*[18], Kesari *et al*[23, 24], Walbert *et al*[22] and Gilbert *et al*[19] examined the effect of CEL in combination with drugs with or without TMZ. The data presented by Reardon *et al*[18], Walbert *et al*[22] and Gilbert *et al*[19] showed some promising results.

Levin *et al*[16] used the combination of 13-cis-retinoic acid and CEL. Based on experimental studies, it was expected that the combination would result in further suppression of COX-2 expression; however, it did not result in PFS rate improvements in patients. Interestingly, the use of 13-cis-retinoic acid alone was apparently more effective. This may be due to the limited population or anonymous intracellular feedback loop in response to this combination[16].

In the study by Reardon *et al*[18] the combination of CEL with irinotecan was used in patients with recurrent GBM after heavy pretreatment. This combination is expected to be safe and have synergistic effects[18, 29]. But for any kind of recommendation, more evaluation is needed.

Kesari *et al*[23] (2007), found that the four-drug regimen (etoposide, cyclophosphamide, thalidomide and CEL) was not as effective as expected. The sample size was too small to analyze clinical characteristics of patients in each subgroup. The inhibitory effect of anti-angiogenesis drugs on tumor growth may take time. Therefore, addressing the McDonald's criteria alone may lead to an incorrect assessment of the effectiveness of the metronomic regimen. It should also be noted that the patients included in this study were seriously sick and under large tumor burden. This regimen may be more effective in patients with better prognosis[23].

The patients in the study by Kesari *et al*[24] which was published in 2008 received TMZ only as an adjuvant drug in combination with thalidomide and CEL; however, the benefits of concomitant and adjuvant use of TMZ with radiotherapy have been clarified[24, 30]. The patients were involved in the study after radiotherapy and had stable disease therefore good prognosis. In this study, researchers couldn't correlate response with MGMT status because of their inability of extracting high-quality DNA from archival specimens. All of these limitations may affect the reported results[24].

Marta Penas-Prado *et al*[20] couldn't demonstrate any benefit from combination of three or four drugs (isotretinoin, CEL, thalidomide and dose-dense TMZ) in patients with GBM. In contrast with earlier studies, they have shown that adding isotretinoin to the regimen can have negative effects. Unbalanced inclusion of patients with true tumor progression into different arms may affect the interpretation of results.

In Walbert *et al*[22] study, combination therapy with 6-thioguanine, capecitabine, and CEL with lomustine or TMZ showed promising results in patients with high-grade Anaplastic glioma (AG) but not in those with recurrent GB. However, the number of included patients did not meet the determined sample size.

In the trial published by Gilbert *et al*[19] (2010), primitive data on adjuvant system of thalidomide, isotretinoin and CEL showed potential benefit as well as higher incidence of adverse reactions; however, the number of patients in each investigational arm was limited.

Other related objects

GB metastasis is rare but can occur. In clinical cases reported by Seiz *et al*[3], it has been shown that there are possible factors related to surgical procedures and following treatments which could result in far-distant metastases of GB. Four patients were examined in this study. They administered a 2-drug TMZ + CEL regimen to patients and then observed that anti-angiogenic therapy would increase the potential of tumor metastases[3]. Possible reasons may include overexpression of EGFR under hypoxic situations[31], transforming growth factor beta (TGF-β) triggered invasion[32] and overexpression of tyrosine kinase Axl[33]. Therefore, despite the positive local effects of anti-angiogenic therapy, it should be noted that this can lead to tumor cells metastasis[3].

CEL plays a functional role in the reduction of brain edema development following intra-cerebral hemorrhage (ICH)[34]. Dexamethasone has been used traditionally to manage cerebral edema. It is

now believed that restricting the administration of glucocorticoids may improve patients' clinical outcome[35, 36]. Rutz *et al*[37] reported one neuro-oncological case in this regard. They used CEL rather than dexamethasone in a patient with GBM to prevent brain edema. Cerebrospinal fluid (CFS) and serum concentrations of CEL were determined. CFS concentration was 54 times lower than serum concentration. On the other hand, CEL has been shown to be clinically useful. TMZ was the main chemotherapy agent in this study. As a result, adding CEL to TMZ was effective to prevent brain edema. The case studied by Rutz *et al*[37] successfully did not require dexamethasone administration.

The management of seizure in brain tumor is important. One of the drugs of choice for this purpose is phenytoin. In a clinical trial conducted by Grossman *et al*[21] (2007), the effect of phenytoin, as an EIASD, on CEL was investigated. Phenytoin did not affect CEL pharmacokinetics parameters significantly. Therefore, the combination of them would be acceptable.

CONCLUSIONS

Based on the results of 12 included clinical trials and 690 eligible patients, it seems that CEL could be administered in the treatment protocol of GB as an adjuvant agent. In conclusion, the use of CEL in the elderly and patients with more comorbidities seems more reasonable to improve their quality of life. Also, given that no serious side effects of CEL were reported, it is safe to be used in different regimens. Nevertheless, if we want to be more specific about the position of CEL in GBM treatment, further clinical studies with reasonable sample sizes are required.

Conflict of Interests:
The authors indicated no potential conflicts of interest.

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