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Review

Efficacy and Safety of Carmustine Wafers in the Treatment of Glioblastoma Multiforme: A Systematic Review

Glioblastoma Multiforme Tedavisinde Karmustin Gofretlerinin Etkinlik ve Güvenirliği: Sistematik Bir Derleme

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ABSTRACT

The aim of this study was to a conduct a systematic review of carmustine wafers (Gliadel wafers) for the treatment of glioblastoma multiforme (GBM) to assess the survival benefit and safety of this therapy. The inclusion criteria were 1) prospective or retrospective clinical trial; 2) patients who had undergone resection for primary GBM or first recurrence of GBM with or without carmustine wafer implantation; 3) patients with malignant gliomas that included GBM; 4) outcomes including survival analysis of the GBM population. Six trials met the inclusion criteria; four were randomized, controlled trials and two were retrospective. The trials varied with regard to the type of patients and interventions. In three of the trials, patients with GBM who received carmustine wafers had significantly longer median survival than patients who did not receive wafers. Implantation of carmustine wafers did not significantly improve progression-free survival. Carmustine wafers did not increase adverse effects. This systematic review suggests that carmustine wafers have demonstrated promise as an effective and tolerable treatment in comparison to other treatment strategies in patients with GBM.

KEYWORDS: Glioblastoma multiforme, Carmustine wafers, Gliadel wafers, BCNU wafers

ÖZ

Çalışmanın amacı, glioblastoma multiforme (GBM) tedavisinde karmustin gofretlerinin (Gliadel gofretleri) bu tedavinin sağkalıma faydası ve güvenirliğini değerlendirmek üzere sistematik bir gözden geçirmesini yapmaktı. Çalışmaya alma kriterleri şöyleydi: 1) prospektif veya retrospektif klinik çalışma; 2) primer GBM için rezeksiyon yapılmış hastalar veya karmustin gofret implantasyonu ile veya olmadan ilk GBM öyküsü; 3) GBM dahil malign gliomlu hastalar; 4) GBM popülasyonunda sağkalım analizi dahil sonuçlar. Çalışmaya alma kriterlerini altı çalışma karşıladı; bunların dördü randomize kontrollü çalışmalar ve diğer ikisi retrospektifti. Çalışmalar hasta tipi ve girişimlerine göre farklılık gösteriyordu. Çalışmaların üçünde karmustin gofretleri alan GBM hastalarında medyan sağkalım gofret kullanılmayan hastalardan önemli ölçüde daha uzundu. Karmustin gofretleri implantasyonu progresyonsuz sağkalımı ve yan etkileri önemli ölçüde artırmadı. Bu sistematik derleme karmustin gofretlerinin GBM hastalarında diğer tedavi stratejileriyle karşılaştırıldığında etkin ve tolere edilebilir bir tedavi olarak ümit verdiklerini göstermiştir.

ANAHTAR SÖZCÜKLER: Glioblastoma multiforme, Karmustin gofretleri, Gliadel gofretleri, BCNU gofretleri

INTRODUCTION

Glioblastoma multiforme (GBM) has been reported to be the most frequently occurring primary central nervous system tumor (1). In the United States and European countries, about 3 in 100,000 people have newly diagnosed GBM (1). These newly diagnosed GBMs account for more than 51% of all gliomas (1). The World Health Organization (WHO) grading system for gliomas, which is based on the histological characteristics of the tumor, ranges from grade I, least malignant, to grade IV, most malignant (1). Glioblastoma multiforme is categorized as grade IV.

To improve survival of patients with GBM, the standard treatment of care consists of initial surgical resection of the tumor followed by radiotherapy and subsequently chemotherapy (17). Survival rates for men and women are similar, but younger patients have better survival rates than older patients (6). Five-year survival rates in the National Cancer Institute population databases are about 13% in patients ranging in age from 15-45 years but only 1% in patients aged 75 years and older (6).

About 40 years ago, nitrosoureas including 1.3-bis (2chlorethyl)-1-nitrosourea (carmustine) were first used for the treatment of gliomas (10). Their efficacy was moderate

but doses that produced response rates up to 50% caused severe systemic side effects (10). A few years later, polymers were developed that could in theory deliver chemotherapy beyond the blood-brain barrier, and subsequently biodegradable polymers that permitted more constant drug delivery became available and such polymers were used to create the carmustine wafer (Gliadel wafer, BCNU wafer) (10).

Several studies have found that carmustine wafers provide a survival benefit for patients with GBM. A meta-analysis published in 2007 found that treatment with carmustine wafers and temozolomide (TMZ) was more effective in improving survival than no chemotherapy (13). It was concluded that the clinical benefits of the treatment appeared to extend up to 24 months. A systematic review of Gliadel wafers used for the treatment of malignant glioma, which was also published in 2007 and included three randomized controlled trials (RTCs) and one prospective cohort study, found that two RTCs reported that patients with newly diagnosed malignant glioma who were treated with Gliadel wafers had a significant survival benefit compared with the control group (12). A study published in 2011 found that two RCTs that assessed the effectiveness of Gliadel wafers for treating patients with high-grade glioma found that compared with placebo the wafer improved survival without increasing the incidence of adverse effects (5).

The aim of this systematic review was to assess the survival benefit and safety of Gliadel wafers compared with placebo or alternative treatment in patients with GBM.

METHODS

Search Strategy

We performed a search using the following databases in December 2012: PubMed, Google Scholar, Biomedical Central. The search terms used were the following: glioblastoma multiforme, adjuvant, carmustine or BCNU, wafers, radiotherapy or surgery; primary or recurrent. We also searched the ASCO meeting website for relevant trials. The reference lists of the clinical trials identified were searched to identify additional trials. Using these search methods, a total of 149 records were identified (Figure 1). Next, the abstracts of the identified studies were screened for relevancy and duplicate patient databases. This resulted in 134 records being excluded, leaving 15 records (Figure 1).

Selection of Studies

Review studies had to meet the following criteria to be included in this systematic review: 1) prospective or retrospective clinical trial; 2) patients who had undergone resection for primary GBM or first recurrence of GBM with or without receiving Gliadel wafer implantation; 3) patients with malignant gliomas that included GBM; 4) outcomes including survival analysis of the GBM population.

Studies were excluded if 1) patients had malignant gliomas but not GBM; 2) the study was not carried out to investigate the efficacy of carmustine wafer therapy; 3) the outcomes did not include survival analysis.

Data Extraction

The following data were extracted: study design, disease type, type of intervention, percentage of patients with GBM, percentage of male patients, Karnofsky performance score, median survival for GBM subgroup, survival rate, median progression-free survival, progression-free survival rate, duration of follow-up, and adverse events. The data were extracted from eligible studies by two independent reviewers. In instances where the two reviewers did not agree, a third reviewer was consulted to resolve the disagreement.

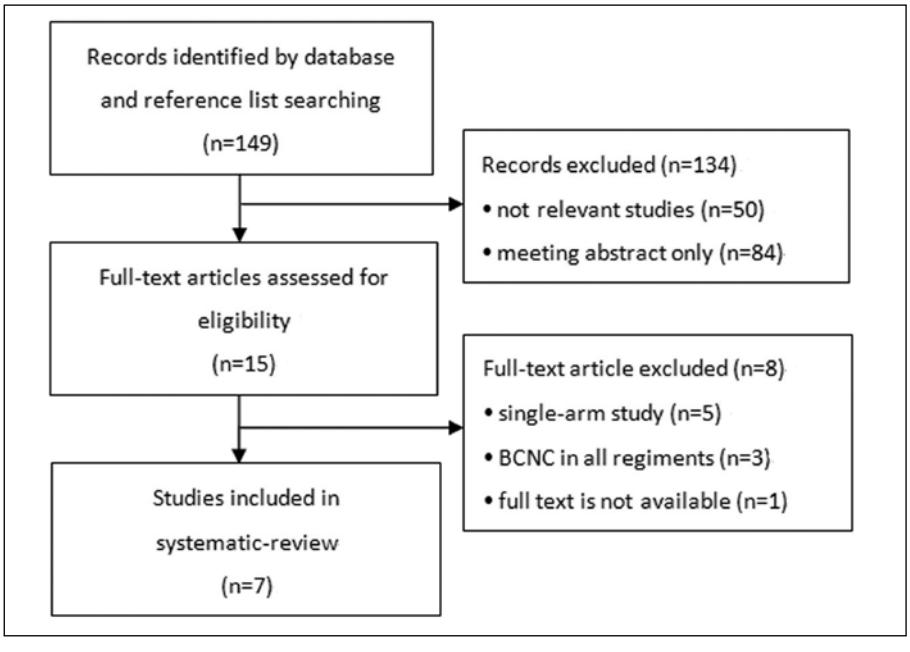

Figure 1: Flow diagram of study selection.

Outcome Measures

The primary outcome of the systematic review was median survival. Secondary outcomes were survival rate, median progression-free survival, and progression-free survival rate. Adverse events were reported and categorized.

RESULTS

Selection of Trials

Our search strategy resulted in seven papers being included in our systematic review (Figure 1) (4, 8, 9, 11, 14-16). These seven papers included six different trials; one trial was presented in two papers, one analyzing the short-term results and the other analyzing the long-term follow-up results (15, 16). Three of the studies were RCTs (4, 8, 14-16) and two trials were retrospective (9, 11). The characteristics of the trials and types of patients are presented in Table I.

Disease Type

The patients studied with regard to disease type varied among the trials. All the trials only included patients with newly-diagnosed tumors except for the study by Kunwar et al. in which all patients had first recurrence of GBM (8) and the study by Brem et al. in which patients had malignant recurrent brain tumors (4). The study by McGirt et al. was the only trial that only included patients with newly diagnosed GBM (9). The trial conducted by Westphal et al. included patients with malignant glioma (15, 16), and the studies by Valtonen et al. and Noël et al. included patients with Grade III and IV glioma (11, 14).

Type of Intervention

In the study by Valtonen et al., one group of patients (68% GBM) was treated with Gliadel wafers and another group (100% GBM) was administered placebo wafers (14). Similarly, in the study conducted by Westphal et al. there was a Gliadel wafer group (84.2% GBM) and a placebo wafer group (88.3% GBM) (15, 16). In the study by Brem et al., patients (65.3%) were randomly assigned to surgery with Gliadel wafers or placebo wafers (4). Kunwar et al. compared patients treated with Gliadel wafers with those treated with IL13-PE38QQR (cintredekin besudotox) (8). In the study by McGirt et al., a group treated with the combination of Gliadel wafers and TMZ was compared with a group treated with TMZ alone (9). Noël et al. compared patients (71.4% GBM) treated with chemoradiotherapy followed by adjuvant chemotherapy with Gliadel wafers with patients (43.2% GBM) treated with chemoradiotherapy followed by adjuvant chemotherapy without Gliadel wafers (11).

Overall Survival

Six papers included data on median survival (Table II). Patients with GBM who received Gliadel wafers were found to have significantly longer median survival in the studies of Valtonen et al., Westphal et al., and McGirt et al. (9, 14, 16). Kunwar et al., and Noël et al. did not find that Gliadel wafers significantly increased median survival in patients with GBM (8, 11). In the trial by Brem et al., Gliadel wafers lowered the risk of death with an estimated hazard ratio of 0.8 (P=0.22) in the GBM subgroup analysis that included 145 patients (4).

Table I: Characteristics of Trials and Patients

Study	Study design	Disease type	Type of Intervention	Patient number	GBM n(%)	Male (%)	KPS
Valtonen 1997 (14)	RCT	Primary Grade III and IV glioma	GW vs. Placebo	16 vs. 16	11 vs. 16 (68.8 vs. 100)	50 vs. 37.5	75 vs. 90 (Median)
Westphal 2003 (16)	RCT	Primary malignant glioma	GW vs. Placebo	120 vs. 120	101 vs. 106 (84.2 vs. 88.3)	63.3 vs. 70.0	NA
Westphal 2006 (15)	RCT	Primary malignant glioma	GW vs. Placebo	120 vs. 120	101 vs. 106 (84.2 vs. 88.3)	63.3 vs. 70.0	NA
Brem 2005 (4)	RCT	Recurrent malignant glioma	GW vs. Placebo	110 vs. 112	72 vs. 73 (65.5 vs. 65.2)	67 vs. 62	77.0 vs. 74.6 (mean)
Kunwar 2010 (8)	RCT	Recurrent GBM	GW vs. IL13-PE38QQR	93 vs. 183	93 vs. 183 (100 vs. 100)	69.9 vs. 66.1	87.7 vs. 86.9 (Mean)
McGirt 2009 (9)	Retrospective	GBM	GW+TMZ vs. TMZ	30 vs. 45	30 vs. 45 (100 vs. 100)	60 vs. NA	80 vs. NA (Median)
Noël 2012 (11)	Retrospective	Primary Grade III and IV glioma	GW vs. non-GW	28 vs. 37	20 vs. 16 (71.4 vs. 43.2)	53.6 vs. 40.5	NA

RCT: *randomized controlled trial;* ***GW:*** *Gliadel wafer;* ***GBM:*** *glioblastoma multiforme;* ***KPS:*** *Karnofsky performance score;* ***TMZ:*** *temozolomide;* ***RT:*** *radiotherapy;* ***NA:*** *not available.*

Table II: Summary of Efficacy

Study	Type of Intervention	Median survival (mo) for GBM subgroup	Survival rate (%)	Median PFS (mo)	PFS rate (%)	Follow-up (mo)
Valtonen 1997 (14)	GW vs. Placebo	53.3 vs. 39.9 (P= 0.008)	NA	NA	NA	24
Westphal 2003 (16)	GW vs. Placebo	13.5 vs. 11.4 (P=0.04)	59.2 vs. 49.6 (1 yr);	5.9 vs. 5.9 (P=0.9)	NA	12-30
Westphal 2006 (15)	GW vs. Placebo	13.1 vs. 11.4 (P=0.08)	59.2 vs. 49.6 (1 yr); 15.8 vs. 8.3 (2 yr); 9.2 vs. 1.7 (3 yr, P=0.01)	NA	NA	56
Brem 2005 (4)	GW vs. Placebo	NA	56 vs. 36 (6 mo; P=0.02)	NA	NA	
Kunwar 2010 (8)	GW vs. IL13-PE38QQR	8.8 vs. 9.1 (P=0.476)	NA	NA	NA	NA
McGirt 2009 (9)	GW+TMZ vs. TMZ	20.7 vs. 14.7 (P < 0.01)	NA	NA	NA	18±10
Noël 2012 (11)	GW vs. non-GW	20.8 vs. 13.8	95 vs. 81.3 (6 mo)[a] 75 vs. 62.5 (1 yr)[a]; 38.9 vs. 0 (2 yr)[a] (P=0.067)	9.7 vs.7.8[a]	73.7 vs. 64.6 (6 mo)[a] 36.8 vs. 32.2 (12 mo)[a] 27.6 vs. 21.5 (18 mo)[a] (P=0.4)	17.1

***GBM:** glioblastoma multiforme; **PFS:** progression free survival; **RFS:** relapse free survival; mo: month; **yr:** year; **a:** for GBM subgroup.*

Only the two papers by Westphal et al., the paper by Noël et al., and the paper by Brem et al. compared the survival rate between groups. In the initial report by Westphal et al., the survival rate was not significantly better for GBM patients who received Gliadel wafers compared with GBM patients given placebo (16). In the follow-up study by Westphal et al. the 1- , 2- and 3-year survival rates were calculated and at 3 years the patients who received Gliadel wafers had a significantly better survival rate than those who received placebo (15). Noël et al. calculated survival rates at 6 months, 1 year, and 2 years for the subgroup of patients with GBM and found no significant differences in survival rates between those who did and did not receive Gliadel wafers (11). Brem et al. found that Gliadel wafers significantly improved survival at 6 months (4).

Progression-Free Survival

Data on median progression-free survival were calculated in the initial study by Westphal et al. and in the study by Noël et al. (11, 16). There was no significant difference in progression-free survival between patients given Gliadel wafers and those given placebo in the study by Westphal et al. (16). Also, Noël et al. did not find a significant difference between GBM patients who received Gliadel wafers and those who did not (11). Only in the study by Noël et al. was the progression-free survival rate reported. They found that there was no significant difference at 6, 12 and 18 months in the rates for GBM patients who did and did not receive Gliadel wafers (11).

Adverse Events

Only Valtonen et al., Westphal et al. in their initial paper, Kunwar et al., and Brem et al. reported the incidence of adverse events (4, 8, 14, 16). The incidence of adverse events in these studies is summarized in Table III. Westphal et al. found no significant difference in events between the groups except for intracranial hypertension being more common at 6 months after surgery in the Gliadel wafer group, a result they attributed to recurrence of the primary tumor rather than to the wafers (16). The only significant difference in adverse events between the groups in the study by Kunwar et al. was that pulmonary embolism was more common in the group that received IL13-PE38QQR (8).

DISCUSSION

Our search strategy identified six trials of carmustine wafers for treating primary or first recurrence of GBM in which survival analysis was included. In two trials that also included patients with WHO Grade III glioma (11, 14), we extracted the data from subgroup analysis of GBM. The carmustine wafers were compared with placebo in three trials (4, 14, 16) and they were compared with a different treatment that did not include the wafers in another three trials (8, 9, 11). Our review revealed three trials in which patients with GBM who received carmustine wafers had statistically significant longer overall survival (9, 14, 16). Survival rate data were only reported in three trials (3, 15, 16) and the patients who received the

Table III: Summary of Adverse Events

Adverse event (%)	Valtonen 1997 (GW vs. Placebo)	Westphal 2003 (GW vs. Placebo)	Brem 2005 (GW vs. Placebo)	Kunwar 2010 (GW vs. IL13)
Nervous system				
Abnormal gait		5 vs.5		0.5 vs. 0.3
Amnesia		9.2 vs.10		
Aphasia		17.5 vs. 18.3		1.6 vs. 1.2
Ataxia		5.8 vs. 4.2		
Brain edema		22.5 vs. 19.2		0.2 vs. 0.3
Confusion		23.3 vs 20.8		
Convulsion	19 vs. 13	33.3 vs. 37.4		
Depression		15.8 vs. 10.0		
Dizziness		5.0 vs. 9.2		
Facial paralysis		6.7 vs. 4.2		
Grand mal convulsion		5.0 vs. 4.2		
Headache				0.3 vs. 0.4
Hemiplegia		40.8 vs. 44.2		0.5 vs. 0.3
Hemiparesis	38 vs. 25			1.5 vs. 0.8
Incoordination		2.5 vs. 6.7		0.2 vs. 0.3
Intracranial hypertension		9.2 vs. 1.7		
Intracranial infection			3.6 vs. 0.9	
Monoparesis				0.2 vs. 0.5
Mental status change				0.1 vs. 0.3
Neuropathy		6.7 vs. 10.0		
Seizure			37.3 vs. 28.6	
Speech disorder		10.8 vs. 8.3		
Vascular system				
Anemia			7 vs. 11	
Deep vein thrombosis				0.2 vs. 0.5
Thrombocytopenia			2 vs. 2	

GW: *Gliadel wafer.*

carmustine wafers had a significantly better overall survival rate in two of these trials. The incidence of events was similar in the two groups in all four trials that reported on adverse events (8, 14, 16). Overall results of these trials seem to suggest that carmustine wafer implantation demonstrates promise as an effective and tolerable treatment strategy for GBM.

Several other studies that did not meet our criteria for inclusion in this systematic review reported on survival of patients with GBM who received carmustine wafers. In a single-arm study, Bock et al. enrolled 44 patients with newly diagnosed GBM. All patients received carmustine wafers and concomitant radiochemotherapy (3). The median overall survival was 12.7 months and median progression-free survival was 7.0 months. In another single-arm study, Kleinberg et al. analyzed data for 46 patients with newly diagnosed malignant glioma (87% with GBM) who received carmustine wafers followed by radiotherapy (7). The median survival for the patients with GBM was 12.8 months. Attenello et al. retrospectively reviewed the records of 1013 patients with WHO grade III or IV malignant glioma (2). A total of 288 patients received carmustine wafers. Patients with GBM who received the wafers had a median survival of 13.5 months and a 2-year survival rate of 20%. In all four studies the median survival was about 13 months for patients with GBM who had implantation of carmustine wafers.

Previous systematic reviews of studies that focused on the use of carmustine wafers in patients with GBM were carried out by Perry et al. and Hart et al. (5, 12). The goal of the systematic review of Hart et al. was to assess the clinical effectiveness of the wafers and the goal of the systematic review by Perry et al. was to assess overall survival, adverse events, and quality of life. Hart et al. identified two RCTs in which carmustine

wafers were compared with placebo and patients afterwards received radiotherapy and concluded that wafer implantation significantly improved survival without causing an increase in adverse events when compared with placebo. Perry et al. included two RCTs with patients who had newly diagnosed GBM and in both studies it was found that the wafers provided a significant survival benefit. Spiegel et al. performed a meta-analysis to assess the effect of adjuvant chemotherapy for GBM (13). They identified 16 trials in which adjuvant chemotherapy was compared with no therapy. Three of the trials included local therapy. The patients received carmustine wafers in two trials while cisplatin was used in one trial. The subgroup analysis of local therapy included all three trials. In our study, we focused on the efficacy and safety of Gliadel wafers for treating patients with GBM.

We found that the percentage of adverse events in the four studies that reported these findings was similar between the two treatment groups in each study. However, there was a large variation among the studies in the percentage of adverse events and this might be attributable to the different type of tumors (e.g., newly diagnosed vs recurrent) and differences in interventions.

We found differences in the definition of median survival among the five trials. Valtonen et al. and McGirt et al. defined survival as the time from surgery to death (9, 14). Westphal et al. and Kunwar et al. defined survival as the time from randomization until death or last known time the patient was alive (8, 16). In the study by Noël et al., survival was defined on the basis of the time after diagnosis by histopathological examination (11). Our review also revealed that the definitions of progression-free survival differed among the two studies that reported this outcome. Westphal et al. used progression-free survival whereas Noël et al. used relapse-free survival (11, 16).

Our systematic review of the efficacy and safety of carmustine wafers in patients with GBM was limited because the studies we identified with our search strategy varied in the type of interventions used and the types of diseases selected for study inclusion. Also, there were differences in the definitions of overall survival and progression-free survival among the studies. In addition, not all studies reported the survival rate, median progression-free survival rate, progression-free survival rate, or percentages of adverse events.

In conclusion, our systematic review suggests that carmustine wafers show promise as an effective and tolerable treatment compared with other treatment strategies in patients with GBM. The use of carmustine wafers as monotherapy or in combination therapy for treating patients with GBM warrants further investigation in larger, randomized controlled trials.

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