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ORIGINAL RESEARCH

Glioblastoma treatment patterns, survival, and healthcare resource use in real-world clinical practice in the USA

Allicia C Girvan[1], Gebra C Carter[1], Li Li[1], Anna Kaltenboeck[2], Jasmina Ivanova[2], Maria Koh[2], Jessi Stevens[2], Eleanor Hayes-Larson[2], and Michael M Lahn[1]

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Abbreviations

FDA, Food and Drug Administration; GB, glioblastoma; GO Project, Glioma Outcomes Project; NCI, National Cancer Institute; NCCN, National Comprehensive Cancer Network; SD, standard deviation

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Abstract

Background: Glioblastoma (GB) treatment remains challenging because of recurrence and poorly defined treatment options after first-line therapy. To better understand real-world application of treatment paradigms and their impact on outcomes, we describe patterns of treatment, outcomes, and use of cancer-related healthcare resource for glioblastoma in the USA.

Methods: A retrospective, online chart-abstraction study was conducted; each participating oncologist contributed ≤5 charts. Patients were ≥18 years with biopsy-confirmed primary or secondary newly diagnosed GB on or after 1 January 2010, had received first- and second-line therapies, and had information collected for ≥3 months after initiation of second-line therapy or until death. Assessments were descriptive and included Kaplan–Meier analyses from initiation to end of second-line therapy, disease progression, or death.

Results: One hundred sixty physicians contributed information on 503 patient charts. During first-line therapy, patients most commonly underwent temozolomide monotherapy (76.5%). During second-line therapy, patients most commonly underwent bevacizumab monotherapy (58.1%). Median duration of second-line therapy was 130 days; median time to disease progression was 113 days. Median survival was 153 days. Use of supportive care was observed to be numerically higher in first- compared with second-line therapy except for anti-depressants, growth factors, and stimulants. Frequently used resources included corticosteroids (78.8% of patients in first-line and 62.6% in second-line therapies), anti-epileptics (45.8% and 41.5%) and narcotic opioids (45.3% and 41.4%).

Conclusions: Most GB patients received temozolomide during first-line therapy and bevacizumab monotherapy or combination therapy during second-line therapy. Use of supportive care appeared to be higher in first- compared with second-line therapy for some agents.

Keywords: treatment patterns, observational, bevacizumab, glioblastoma, first-line therapy, second-line therapy, cancer, temozolomide.

Introduction

Glioblastoma (GB) is the most common and aggressive primary malignant tumor of the brain in adults in the USA. More than 10,000 new cases of GB are diagnosed each year, and ≈50,000 patients have GB [1,2]. From 1995 to 2007, overall survival in the USA was ≈35% for 1 year and <5% for 5 years [2,3]. Treatment of GB imposes an economic burden; patients with malignant brain tumors have been shown to accrue healthcare costs that are 20-fold greater than those of people without cancer [4].

Standard of care for newly diagnosed patients is resection followed by a combination of radiation and temozolomide therapy [5,6]. Aggressive therapy in newly diagnosed patients has improved median overall survival [5,7–11], but recurrence is common in almost all patients and the prognosis remains poor [7,11]. After first-line therapy of recurrent disease, standard of care is not well defined and is often patient-dependent, and options are limited [12–14]. Advances in care have resulted in only incremental improvements in overall survival [9,10]. Hence, efforts are needed to define effective strategies to treat GB, particularly during recurrence.

In this retrospective study, we explore real-world treatment patterns and outcomes for GB to better understand GB treatment paradigms in the USA. In patients with newly

diagnosed GB who had received first- and second-line therapies, we wanted to describe demographics and clinical characteristics at the diagnosis, treatment patterns (including specific agents used in lines of therapy, duration of therapy, and disease progression by line of therapy), incremental improvement in survival since initiation of second-line therapy, prognostic markers and symptoms, and GB-related use of healthcare resources. Better understanding of these patient characteristics and treatment outcomes may help clarify the potential contributions of new treatments for GB.

Methods

Study design

This was a retrospective, observational study in which oncologists contributed de-identified information from patient charts in clinical practice through an online data-collection form during December 2012. The study collected information on physicians and patients. Physicians were selected randomly from a panel of practicing oncologists and invited to participate. Each physician had at least one GB-diagnosed adult patient who had received second-line systemic therapy.

To ensure that patients were selected randomly, oncologists were provided with a randomized letter of the alphabet. Oncologists were asked to pull the chart for the first patient with a surname beginning with the designated letter. If none of the patients whose surname began with the designated letter met the criteria for the study, oncologists continued to the next letter of the alphabet. Physicians could contribute up to five patient charts; collection of 500 charts was intended.

Patients were ≥18 years of age with a diagnosis of primary or secondary GB confirmed by biopsy on or after 1 January 2010 and no later than 31 December 2012. Collection of patient data was restricted to those who received first-line therapy and second-line systemic therapy and who had information collected for ≥3 months after initiation of second-line systemic therapy or until death. Adjuvant therapy using temozolomide after radiation therapy in combination with temozolomide was considered to be part of first-line therapy. Patients with malignant primary tumors other than glioma or astrocytoma were excluded.

Statistical analyses

For the characteristics of physicians and patients, frequencies and percentages were reported for categorical variables. Mean, standard deviation (SD), and median values were reported for continuous variables. Median time from initiation of second-line therapy to discontinuation because of disease progression or death (accounting for censoring) was estimated by Kaplan–Meier analyses. Time from end of first-line to initiation of second-line therapy was described by univariate analyses (mean, median, SD).

Results

Physician characteristics

160 physicians with a mean (SD) of 20.2 (32.6) patients with GB per physician contributed to a study sample of 503 patient charts (mean [SD] 3.1 [1.8] patient charts per physician). Overall prevalence of physician access/participation was 19%. Physicians had a mean (SD) of 13.8 (6.7) years of practice. 113 (70.6%) physicians specialized in general oncology and 47 (29.4%) in neuro-oncology. Practices were located in the northeastern (33.1%; n=53), southern (29.4%; n=47), western (20.0%; n=32), and midwestern (17.5%; n=28) regions of the USA. 75 (46.9%) physicians were affiliated with teaching hospitals, and 34 (21.3%) were affiliated with comprehensive cancer centers designated by the National Cancer Institute (NCI). Practice settings were: office-based separate from hospitals or foundations (52.5%; 84 physicians), office-based owned by hospitals or foundations (26.3%; n=42), hospitals (12.5%; n=20), community settings (8.8%; n=14).

Patient characteristics

Overall mean patient age at the diagnosis of GB was 58.4 years (Table 1). Most patients were male (68.6%) and Caucasian (74.0%). The mean Charlson Comorbidity Index [15,16] at the diagnosis (which excluded malignancies) was 0.65. Hypertension was present in 32.4% of patients, depression in 13.1%, anxiety in 11.5%, and diabetes mellitus without chronic complications in 9.3%. Almost all tumors (97.8%) were primary GB; 40.2% were parietal, and 29.2% were frontal.

Prognostic biomarkers

Fewer than 25% of patients were assessed for each prognostic biomarker. The O6 methylguanine–DNA–methyltransferase promoter was assessed in 22.5% of all patients, of whom 47.8% (n=54) tested positive. The epidermal growth factor receptor (EGFR) or EGFR variant III was assessed in 16.3%, of whom 42.7% (n=35) tested positive, and the isocitrate dehydrogenase 1 mutation was assessed in 9.7%, of whom 36.7% (n=18) tested positive.

Systemic therapy for GB

There was a mean (SD) of 434 (230) days of post-diagnosis follow-up. After the diagnosis, 94.8% of patients received radiation therapy at any time. Primary surgery after the diagnosis included biopsy (28.2%) and resection (68%); 87.1% of resections (n=298) excluded carmustine implants. Subsequent surgeries were conducted in 4.4% of patients (n=22), and a maximum of three surgical procedures after primary surgery occurred after the diagnosis of GB.

By design, all patients received first- and second-line therapies, and of those who received active second-line therapy,

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Table 1. Patient characteristics.

Characteristic	All patients (N=503)
Demographic information	
Age (years) at GB diagnosis, mean (SD)	58.4 (11.8)
Male, n (%)	345 (68.6)
Race and ethnicity, n (%)	
White	372 (74.0)
Black or African–American	83 (16.5)
Asian	22 (4.4)
Hispanic or Latino	12 (2.4)
Other[a]	14 (2.8)
Marital status, n (%)	
Married	360 (71.6)
Single	109 (21.7)
Not known	34 (6.8)
GB type, n (%)	
Primary	492 (97.8)
Secondary	11 (2.2)
Primary site of GB tumor, n (%)	
Frontal	147 (29.2)
Parietal	202 (40.2)
Occipital	53 (10.5)
Temporal	78 (15.5)
Unknown and other	23 (4.6)
Charlson Comorbidity Index[b] before and at the diagnosis, mean (SD)	0.65 (1.2)
Comorbidities, n (%)[c]	
Hypertension	163 (32.4)
Depression	66 (13.1)
Anxiety	58 (11.5)
Diabetes mellitus without chronic complications	47 (9.3)
Chronic pulmonary disease	38 (7.6)
Peptic ulcer disease	35 (7.0)
Obesity	32 (6.4)
Myocardial infarction	31 (6.2)
Employment status at the diagnosis, n (%)	
Full-time	183 (36.4)
Part-time	83 (16.5)
Not employed	205 (40.8)
Unknown	32 (6.4)
Health insurance plan at the diagnosis, n (%)	
Private health insurance	263 (52.3)
Medicare	170 (33.8)
Medicaid	57 (11.3)
Uninsured/other	13 (2.6)
Patient has a primary caregiver, n (%)	
Primary caregiver present	361 (71.8)
No primary caregiver	100 (19.9)
Unknown	42 (8.3)
Relationship to primary caregiver, n (%)	
Spouse	270 (53.7)
Child	40 (8.0)
Extended family relative	34 (6.8)
Not a family member/unknown	17 (3.4)

[a]American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other.
[b]Metastatic solid tumors were not included. Comorbidities were included if they were recorded by the physician as occurring at any time before the diagnosis of GB.
[c]Comorbidities with >5% occurrence are listed.
BMI, body mass index; GB, glioblastoma.

only 12 (2.4%) received third-line therapy. During first- and second-line therapies, chemotherapeutic agents were used as monotherapy or in combination (Table 2). The most common agents used for first-line treatment were temozolomide (p.o.; 83.9% of patients overall), bevacizumab (15.3%), and temozolomide (i.v.; 8.9%), and the most common second-line agents were bevacizumab (79.5%), irinotecan (22.5%), and temozolomide (p.o.; 5.8%).

First-line systemic therapy

During first-line systemic therapy, patients most commonly received temozolomide (p.o. or i.v.) as monotherapy (76.5%) or in combination with bevacizumab (9.9%) (Table 2). Chemotherapy was administered concomitant and adjuvant to radiation therapy in 53.5% of patients. Radiographic evidence (43.1%) was used to assess the response to first-line therapy more frequently than clinical assessment (12.9%), though radiographic and clinical assessments were reported for 43.9% of patients. Radiographic response in first-line patients was most often assessed using McDonald criteria (77.8%). Partial response was the most common best response to first-line therapy in 40.8% of patients (Table 3). Disease progression was the most frequently reported reason for ending first-line therapy (57.3% of patients who ended first-line therapy).

Second-line systemic therapy

During second-line therapy, patients most commonly received bevacizumab as monotherapy (58.1%), bevacizumab–irinotecan

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Table 2. Sequence of first- and second-line regimens.

First-line regimen (N=503), n (%)	Temozolomide[a,b]	Temozolomide[a] + bevacizumab	Temozolomide[a] + bevacizumab + other[c]	Temozolomide[a] + other[d]	Other monotherapy or combinations
	385 (76.5)	50 (9.9)	13 (2.6)	12 (2.4)	43 (8.5)
Second-line regimen[e]					
Bevacizumab	246 (63.9)	30 (60.0)	4 (30.8)	1 (8.3)	11 (25.6)
Bevacizumab + irinotecan	70 (18.2)	4 (8.0)	3 (23.1)	3 (25.0)	2 (4.7)
Bevacizumab + temozolomide[a]	10 (2.6)	1 (2.0)	0 (0)	1 (8.3)	0(0)
Bevacizumab + other[f]	5 (1.3)	3 (6.0)	3 (23.1)	0 (0)	3 (7.0)
Irinotecan	20 (5.2)	3 (6.0)	0 (0)	3 (25.0)	3 (7.0)
Temozolomide[a]	20 (5.2)	1 (2.0)	1 (7.7)	0 (0)	11 (25.6)
Other monotherapy or combinations	14 (3.6)	8 (16.0)	2 (15.4)	4 (33.3)	13 (30.2)

[a]Includes p.o. and i.v.
[b]Example: overall, 76.5% of patients were treated with temozolomide during first-line therapy. Of those, 63.9% were treated with only bevacizumab during second-line therapy, and 18.2% had bevacizumab–irinotecan combination therapy.
[c]Other agent(s) combined with temozolomide include carboplatin, chloroquine, cyclophosphamide, cisplatin, irinotecan, lomustine, methotrexate, thalidomide, and polifeprosan 20 with carmustine implant.
[d]Other agent(s) combined with temozolomide + bevacizumab include carboplatin, carmustine, investigational treatment PLX3396, lomustine, irinotecan, and thalidomide.
[e]As a proportion of first-line therapy.
[f]Other agent(s) combined with bevacizumab include carboplatin, carmustine, cisplatin, erlotinib, etoposide, lomustine, investigational treatment PLX3396, and combination irinotecan + temozolomide.

combination therapy (16.3%), or irinotecan monotherapy (5.8%). Of those physicians who prescribed bevacizumab during second-line treatment, 47.5% were affiliated with a teaching hospital, and 21% were affiliated with an NCI-designated comprehensive cancer center.

Radiographic evidence was reportedly used to assess response in 41.4% of patients, whereas clinical assessment was used in 19.1%, and radiographic and clinical assessments were used in 39.5%. As in first-line therapy, the radiographic response was most often assessed using McDonald criteria (76.7%). Stable response was the most common best response to second-line therapy (38.4% of patients) (Table 3). Median duration of second-line therapy was 130 days, median time to disease progression was 113 days, and median duration of survival was 153 days. The most frequently reported reason for ending second-line therapy was disease progression (28.6%).

Sequencing of therapy

Sequencing of therapies in first- and second-line treatments is shown in Table 2. Patients most commonly received temozolomide (p.o. or i.v.) monotherapy during first-line therapy (n=385). Of these, 63.9% during second-line therapy received bevacizumab only, and 18.2% received a bevacizumab–irinotecan combination. Of those who received temozolomide and bevacizumab as first-line therapy (9.9%, n=50), 76% received bevacizumab again in the second-line setting, most commonly as monotherapy (60%, n=30).

Symptoms

During first- and second-line therapies, disease- or treatment-related headaches were reported in 65.8% of patients, neurologic/neurocognitive deficiency in 37.0%, disability in 20.1%, seizures in 20.1%, and pain in 18.9% (Figure 1). During first-line treatment, most symptoms were disease-related rather than treatment-related as reported by the physician. For example, of those with physician-reported symptoms, 89.7% (n=297) of headaches, 86.6% (n=161) of neurologic deficits, and 96.0% (n=97) of seizures were attributed to GB. Disease-related symptoms were also more common than treatment-related symptoms during second-line therapy. Among the three most common symptoms, 90.7% (n=311) of headaches, 94.6% (n=175) of neurologic deficits, and 95.9% (n=117) of disability were attributed to GB rather than second-line therapy.

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Table 3. Duration of survival, response to therapy, and treatment characteristics in first- and second-line therapies.

Overall treatment patterns and characteristics	First-line therapy patients (N=503)	Second-line therapy patients[a] (N=503)
Duration and survival[b]		
Median duration of therapy, days (n=487[c])	—	130
Median time to progression, days (n=304[d,e])	—	113
Median duration of survival, days (n = 487[c])	—	153
Time from first-line to second-line therapy (days), mean (SD) median[f]		77 (132) 24
Best response to therapy, n (%)		
Complete response	84 (16.7)	13 (2.6)
Partial response	205 (40.8)	95 (18.9)
Stable response	104 (20.7)	193 (38.4)
Progression	94 (18.7)	155 (30.8)
Unknown	16 (3.2)	47 (9.3)
Performance status (ECOG), mean (SD)[g]	1.15 (0.7)	1.60 (0.7)
Enrolled in clinical trial, n (%)	6 (1.2)	11 (2.2)
Maximum number of treatment cycles, mean (SD)[h]	5.9 (3.3)	5.6 (3.8)
Reasons for ending therapy among patients who discontinued use of at least one agent, n (%)[i]		
Disease progression	288 (57.3)	86 (28.6)
End conformed to treatment protocol	176 (35.0)	11 (3.7)
Patient refusal to continue treatment protocol	41 (8.2)	12 (4.0)
Adverse event/toxicity	29 (5.8)	9 (3.0)
Lack of benefit	23 (4.6)	7 (2.3)
Cost	8 (1.6)	1 (0.3)
Other, unknown, and missing	24 (4.8)	190 (63.1)

[a]Collection of patient data was restricted to those patients who received first- and second-line therapies.
[b]Measured from start of second-line therapy.
[c]Sixteen patients with invalid death dates were excluded.
[d]Additional patients who ended a therapy for unknown reasons were excluded; four patients' time to progression was censored by death.
[e]Kaplan–Meier analyses were conducted for patients who had ongoing second-line therapy or who ended second-line therapy and gave at least one reason for ending therapy and had a valid death date.
[f]Average number of days from end date of last agent in first-line therapy to start date of first agent administered in second-line therapy.
[g]Karnofsky scores were converted to ECOG scores (ECOG 0 = KS 90–100; ECOG 1 = KS 70–80; ECOG 2 = KS 50–60; ECOG 3 = KS 30–40; ECOG 4 = KS 10–20). Twenty-six patients during first-line therapy and 31 patients during second-line therapy had unknown performance status.
[h]Greatest number of cycles reported for any first- or second-line agent.
[i]If ever reported for any first- or second-line agent. Multiple reasons for ending therapy could have been recorded. Patients with ongoing second-line therapy were excluded.
ECOG, Eastern Cooperative Oncology Group; GB, glioblastoma; KS, Karnofsky score.

Cancer-related use of healthcare resources

Overall, the resources for supportive care used frequently during first- and second-line therapies were corticosteroids (83.0% of patients overall, 78.8% during first-line therapy and 62.6% during second-line therapy), anti-epileptics (50.7%, 45.8%, and 41.5%), narcotic opioids (48.9%, 45.3%, and (41.4%), proton pump inhibitors (47.6%, 45.2%, and 40.0%), and anti-depressants (26.4%, 21.1%, and 23.9%) (Table 4).

Overall, 94.8% of patients received radiation therapy after the diagnosis of GB. Mean (SD) total dose of radiation was

Figure 1. Physician-reported symptoms experienced during first- and second-line therapies. Neuro deficit = neurologic or neurocognitive deficit. The total percentage of patients on first-line therapy experiencing 'other' symptoms was 0.8%, and the total percentage on second-line therapy was 1.4%.

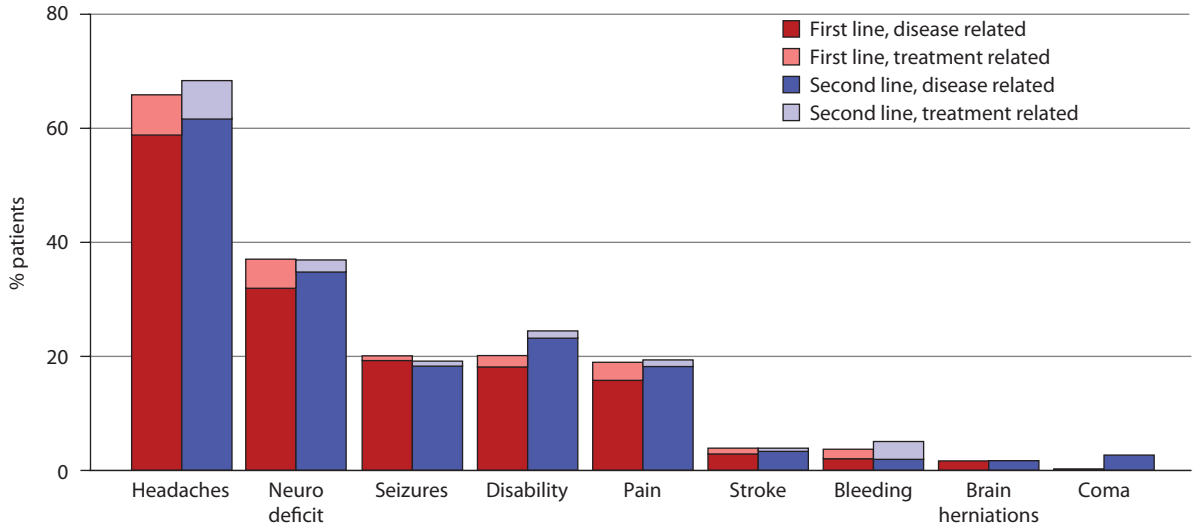

Table 4. Physician-reported use of healthcare resources.

Resource, n (%)	Overall[a,b]	First Line[b]	Second Line[b]
Supportive care			
Corticosteroids	399 (83.0)	379 (78.8)	301 (62.6)
Anti-epileptics	247 (50.7)	223 (45.8)	202 (41.5)
Narcotic opioids	235 (48.9)	218 (45.3)	199 (41.4)
Proton pump inhibitors	232 (47.6)	220 (45.2)	195 (40.0)
Anti-depressants	129 (26.4)	103 (21.1)	117 (23.9)
Growth factors	61 (12.5)	31 (6.4)	40 (8.2)
Transfusions	50 (10.1)	36 (7.3)	26 (5.3)
Stimulants	22 (4.5)	11 (2.2)	18 (3.7)
Inpatient hospitalizations	60 (13.0)	46 (10.0)	23 (5.0)
Oncology clinic/oncologist	383 (99.2)	381 (98.7)	379 (98.2)
Emergency room	104 (44.3)	72 (30.6)	65 (27.7)
Radiotherapist	217 (94.3)	217 (94.3)	58 (25.2)
Palliative care	46 (21.6)	22 (10.3)	41 (19.2)
Pain specialist	27 (13.2)	25 (12.3)	19 (9.3)
Rehabilitation services	75 (39.9)	66 (35.1)	50 (26.6)
General practitioner	64 (42.7)	62 (41.3)	47 (31.3)
Home visits	29 (17.1)	20 (11.8)	20 (11.8)
Skilled nursing facility	11 (6.1)	6 (3.3)	9 (5.0)
Hospice unit stays	27 (13.0)	8 (3.9)	20 (9.7)

[a]'Overall' denotes the number of patients observed for physician-reported use of supportive care in first-line therapy and/or second-line therapy.
[b]Excludes unknowns (observations where physicians could not recall if patient used the service) and third-line resource use.

50.5 (13.6) Gy among patients who received radiation during first- or second-line treatments. During first-line treatment, 84.9% received radiation with a mean (SD) total dose of 50.8 (12.5) Gy. During second-line treatment, 5.0% received radiation with a mean (SD) total dose of 40.2 (15.3) Gy. MRI, CT, and PET were used by 85.3%, 45.5%, and 13.7% during first-line therapy and 79.5%, 32.4%, and 10.3% during second-line therapy, respectively.

Inpatient hospitalizations were reported in 13.0% of patients (10.0% during first- and 5.0% during second-line therapies). Mean (SD) number of inpatient hospitalizations was 1.3 (0.7) per patient with a hospitalization (1.1 [0.3] for first- and 1.2 [0.4] for second-line therapies). The most frequently reported reasons for inpatient hospitalizations were GB-related treatment (43.3% of patients) and management of GB symptoms (40.0%). The emergency room was used by 44.3% (30.6% during first- and 27.7% during second-line therapies). In patients who had undergone a visit to the emergency room, the mean (SD) number of visits was 2.1 (1.6) (1.2 [0.7] for first- and 1.8 [1.3] for second-line therapies). The most frequently reported reason for use of the emergency room was management of GB symptoms (52.9%).

Discussion

In patients with GB, the prognosis is poor and the likelihood of disease recurrence is high. Incremental improvements in therapy have resulted in prolonged survival, but the treatment of GB is not curative. To better understand real-world application of the paradigms of GB treatment in the USA, we described treatment patterns and outcomes in this retrospective chart-abstraction study.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [6] recommend tumor resection followed by radiation and/or temozolomide chemotherapy as first-line treatment, which is the standard of care [5,6]. Patients in the present study most commonly underwent temozolomide (p.o.) monotherapy (76.5%) or temolozamide–bevacizumab combination therapy (9.9%) as first-line therapy. This strategy was consistent with NCCN guidelines and the literature [2,17–20]. In a large population-based study using data on commercial claims, temozolomide was administered as first-line therapy in ≈40% of patients after surgery [21]. In that study, median survival (529 days) was higher in patients receiving neither temozolomide nor radiation therapy compared with temozolomide monotherapy (331 days). The authors postulated that the high median survival of patients with neither treatment may suggest lower-grade tumors for which standard-of-care therapy (radiation therapy with or without temozolomide) did not seem warranted. Inclusion of bevacizumab in combination with temozolomide as first-line therapy in the present analyses may suggest increasing use of bevacizumab [22–25]. In the present analyses, few patients (<5%) were enrolled in clinical trials, thereby highlighting a possible trend in the use of bevacizumab for routine care.

For recurrent disease, according to the NCCN, reoperation should be considered first, followed by chemotherapeutic options beginning with bevacizumab (bevacizumab with/without other chemotherapy, temozolomide, nitrosourea or combination procarbazine/lomustine/vincristine, cyclophosphamide, or platinum-based regimens). For only a subset of patients with recurrent disease, reoperation or repeat irradiation is recommended with or without chemotherapy [6], and additional subgroup recommendations are not available. Thus, recommendations for second-line therapy do not represent a definitive standard of care for recurrent disease and have largely been absent in treatment paradigms, thereby highlighting a pressing unmet treatment need [12–14]. An important finding of these analyses is the use of bevacizumab in GB treatment, particularly during second-line systemic therapy (58.1% of patients received bevacizumab monotherapy in this setting). The US Food and Drug Administration (FDA) provided accelerated approval of bevacizumab as a single agent for patients with GB whose disease progressed after previous first-line therapy but not in newly diagnosed patients [26]. Since the approval of bevacizumab for GB treatment, few studies have described the specific use of bevacizumab for GB treatment outside of clinical trials. Our study confirms the common use of bevacizumab for second-line systemic therapy, suggesting a pattern of second-line treatment for GB in routine care consistent with the indicated use for bevacizumab. Treatment patterns, patient populations, and outcomes may differ depending on the site of care [27,28]. Thus, it is noteworthy that approximately half of the physicians who prescribed bevacizumab during second-line treatment were affiliated with facilities that included teaching hospitals, whereas a lower percentage of physicians who prescribed bevacizumab were affiliated with NCI-designated comprehensive cancer centers.

Some evidence suggests that the use of bevacizumab for the treatment of progressive GB may be associated with prolonged survival. Analyses of the survival of GB patients who died before and after approval of bevacizumab by the US FDA demonstrated that median survival of patients with GB improved after bevacizumab approval [9]. Median survival for patients who died before bevacizumab approval in 2006 and 2008 was 8 months and 7 months, respectively, and median survival for patients who died after bevacizumab approval in 2010 was 9 months.

Incremental advances have been observed in overall survival, but improvements have not been seen across all demographics. Improvement has been observed in patients who received the recommended multidisciplinary treatment of complete resection followed by postoperative radiation therapy [10,29]. However, evidence suggests that not all patients receive recommended treatment [30,31], which may

depend on patient factors and geographic distribution of oncology services. In a study of adult patients in the USA in the Surveillance, Epidemiology, and End Results database, postoperative radiation therapy was less likely in older and unmarried patients, and more likely in patients in higher-income geographic areas or those with a high prevalence of radiation centers [30]. In another study, radiation therapy was less likely in patients with higher age; lower annual income; unmarried status; subtotal resection/biopsy; and African–American, Asian–American, or Hispanic race. However, overall survival improved for patients who received radiation therapy [29]. It has been shown that a six-week delay in radiation therapy reduces median survival by 11 weeks [32]. In the present study, 94.8% of patients received radiation therapy after a diagnosis of GB.

In the Glioma Outcomes Project (GO Project), which assessed patients treated in academic and community practices, only 54% of patients received chemotherapy [33]. Resource use consistent between the GO Project and the present study included MRI (92% use in GO Project, 85% in the present study) and corticosteroid use (99% and 83%, respectively). Use of anti-epileptic medication was more frequent in the GO Project (88% *vs* 51%), and use of anti-depressant medication was more frequent in the present study (26% *vs* 8% in GO Project). Assessment of the frequency of inpatient hospitalizations and emergency-room visits, each 0.2 admissions per month [4], was consistent with that of the present study, which had 1.3 and 2.1 admissions per patient with a hospitalization or visit to an emergency room, respectively.

Symptoms of headaches, neurologic deficit, seizures, disability, and pain were consistent with the literature [34–38]. Some preoperative factors, such as cognitive, language, and motor deficits, have been found to be associated with a poorer prognosis [35]. Venous thromboembolisms have been associated with a higher risk of two-year mortality [39]. Thromboembolisms were not commonly reported in the present study.

Limitations of this study include those typical of chart-abstraction studies. Extent of physician participation was low (19%), which could limit the generalizability of the information. Information obtained from randomly selected physicians may have been different from that obtained from physicians who did not participate, thereby potentially limiting the generalization of study results. Completeness and accuracy of patient information was dependent upon the medical history available to the physician and accuracy of the information transferred by the physician from the patient chart. Due to exclusion of patients censored in the first 3 months after initiation of second-line therapy, survival from initiation of second-line treatment was potentially underestimated, and time to progression and duration of second-line treatment might have been biased. Patients who did not progress to second-line therapy were excluded from the study, thereby limiting generalization of these results to a smaller patient population with GB.

Conclusions

Symptomatic burden and survival represent a pressing unmet need for advanced therapies and therapeutic strategies for patients with GB, particularly during disease recurrence. In this observational study, most patients with GB received temozolomide during first-line therapy and bevacizumab (as monotherapy or in combination with other agents) during second-line therapy. Use of supportive care appeared to be higher in first-line therapy than in second-line therapy with the exception of anti-depressants, growth factors, and stimulants. These analyses suggest potential trends in the treatment of patients with GB in the USA and may aid in the design of future studies to help define effective treatment options for GB.

Contributions

Allicia Girvan, Gebra Carter, Li Li, and Michael Lahn participated in study design. Anna Kaltenboeck, Jasmina Ivanova, Maria Koh, Jessi Stevens, and Eleanor Hayes-Larson were involved in data collection. All authors participated in data interpretation, drafting of the manuscript, and approval of the final version of the manuscript.

Potential conflicts of interest

The International Committee of Medical Journal Editors' (ICMJE) Potential Conflicts of Interests forms for the authors are available for download at: http://www.drugsincontext.com/wp-content/uploads/2015/03/dic.212274-COI.pdf

Allicia Girvan, Gebra Carter, Li Li, and Michael Lahn are employees of and hold stock in Eli Lilly and Co. Anna Kaltenboeck, Anita Chawla, Jasmina Ivanova, Maria Koh, and Jessi Stevens are employees of Analysis Group, Inc. (New York, NY, USA), which received funding from Lilly for the conduct of this study.

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