ORIGINAL RESEARCH

Treatment Patterns, Survival, and Healthcare Costs of Patients with Malignant Gliomas in a Large US Commercially Insured Population

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Background: Glioblastoma multiforme is the most common malignant primary brain tumor in adults and is associated with poor survival rates. Symptoms often include headaches; nausea and vomiting; and progressive memory, personality, or neurologic deficits. The treatment remains a challenge, and despite the approval of multiple new therapies in the past decade, survival has not improved.

Objective: To describe treatment patterns, survival, and healthcare costs of patients with incident glioblastoma in a large US population.

Methods: For this population-based study, adult patients (aged ≥18 years) with incident malignant brain neoplasm who had undergone brain surgery between January 1, 2006, and December 31, 2010, were identified in the Truven Health Analytics MarketScan Research Databases. The patients were stratified into 4 cohorts based on the use of temozolomide and/or external beam radiation therapy within 90 days after brain surgery (ie, the index event). Treatment patterns, survival, and healthcare costs were assessed until patient death, disenrollment, or the end-of-study period.

Results: A total of 2272 patients met the inclusion criteria; of these, 37% received temozolomide and radiation therapy, 13.8% received radiation alone, 3.9% received temozolomide alone, and 45.3% of patients received neither. The average patient age ranged from 55.3 years to 59.8 years across the study cohorts; between 29.8% and 44% of patients in each cohort were female. The duration of temozolomide use was similar between the temozolomide-only cohort and patients receiving temozolomide with external beam radiation; approximately 76% of patients received temozolomide at least 60 days, dropping to 48.1% and 23% at 180 days and 360 days of follow-up, respectively. The median survival was 456 days, ranging from 331 days in the temozolomide-only cohort to 529 days in the cohort that received neither temozolomide nor external beam radiation. The average total costs in the 6 months postindex were $106,896, from $79,099 for patients who received neither temozolomide nor radiation to $138,767 for those who received both therapies.

Conclusion: The survival patterns of patients with glioblastoma seen in this real-world study of current treatments in a clinical setting is similar to the survival rate reported in clinical trials. However, further cost-effectiveness and quality-of-life analyses will be critical to better understand the role of temozolomide therapy in this patient population, considering its considerable cost burden and potential negative impact on survival seen in this study.

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Glioblastoma multiforme is the most common malignant primary brain tumor in adults, with an estimated incidence of 4.43 per 100,000 person-years in the United States and a median age at presentation of 64 years.[1] Glioblastoma multiforme is characterized by seizures; nausea; vomiting; headaches; and progressive memory, personality, or neurologic deficits, as well as treatment resistance.[2] The treatment of glioblastoma multiforme is a challenge, and despite the approval of multiple new therapies in the past decade, survival remains poor.

Based on a national report on the status of cancer published in 2011 in the *Journal of the National Cancer Institute*, the 5-year relative survival rates for glioblastoma multiforme among adults between 2000 and 2006 was only 21.3% for patients aged 20 to 39 years, 5.3% for those aged 40 to 64 years, and only 1.1% for patients aged ≥65 years in the United States.[1] These national 5-year relative survival rates were slightly better when considering all tumors of the neuroepithelial tissue (65.1%, 26.6%, and 4.6% for the same 3 age-groups, respectively).[1]

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The current standard of care for newly diagnosed glioblastoma is derived from a randomized clinical trial published in 2005 and consists of maximal feasible surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide.[3] This treatment regimen, known as the Stupp regimen, has resulted in a median survival of 14.6 months in patients receiving temozolomide therapy alone compared with 12.1 months in patients receiving external beam radiation alone.[3] The adoption of the Stupp regimen has been credited for improvement in the survival of patients with glioblastoma multiforme from 2005 to 2008 compared with the survival from 2000 to 2003, particularly among younger patients.[4,5]

The US Food and Drug Administration (FDA) approved the use of temozolomide for the treatment of glioblastoma multiforme in March 2005. The FDA also approved carmustine wafers (initially in 1997) and bevacizumab (in 2009, for glioblastoma multiforme that has progressed after initial treatment) for the treatment of glioblastoma multiforme, but neither of these treatments has demonstrated a significant role in the upfront treatment of this disease.[6]

The financial costs associated with the addition of temozolomide are significant and have been well documented, particularly in European and Canadian health systems.[7] In the United States, several analyses have underscored the overall costs and burden of out-of-pocket (OOP) costs incurred by patients with glioblastoma multiforme for hospital visits, ancillary care, and drug costs.[8,9] The total expenditures in this patient population have also been described in 2007 by Kutikova and colleagues for 653 patients with primary malignant brain tumors and were estimated at $6364 per month compared with $277 for controls.[9] These costs were mostly associated with inpatient care and likely reflect patient care before the widespread use of temozolomide.[9]

To our knowledge, no study has comprehensively described the total healthcare costs associated with the treatment of glioblastoma and malignant gliomas in the temozolomide era in the United States. We sought to understand the treatment patterns, survival, and economic burden incurred by patients with glioblastoma in clinical practice in the United States. In this study, we used a large commercial claims database and specifically sought to identify a cohort of patients based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) 191.xx codes that most likely represent newly diagnosed glioblastoma to describe patient survival, comorbidities, treatment duration, and healthcare expenditures in the time period after the FDA's approval of temozolomide.

KEY POINTS

- Glioblastoma multiforme is the most common malignant primary brain tumor in adults, and its survival rates remain poor.
- The current standard of care consists of surgical resection followed by radiotherapy, with concurrent and adjuvant temozolomide therapy.
- This is the first study to analyze real-world data related to treatment patterns, costs, and survival trends associated with temozolomide therapy in patients with glioblastoma.
- Total healthcare costs 6 months postindex were highest ($138,767) per patient receiving temozolomide plus radiation and lowest ($79,099) for those receiving neither.
- The median survival time was highest (529 days) in patients who received neither temozolomide nor radiation and lowest (331 days) with temozolomide therapy alone.
- As can be expected, the addition of temozolomide significantly increases the cost of care, and evidence regarding its exact efficacy is limited in this patient population.
- Future cost-effectiveness and quality-of-life analyses are critical to better understand the role of temozolomide in this patient population.

Methods

Data Source and Study Design

Data for this study were gathered and linked from 2 sources: (1) healthcare claims from the Truven Health Analytics MarketScan Commercial and Medicare Supplemental Databases, and (2) the Social Security Administration (SSA) master death files.

The Truven Health databases include fully integrated real-world patient-level data, including pharmacy and medical claims and associated diagnosis and procedure codes, and enrollment data from approximately 25 million lives covered annually by self-insured employers and private health insurance plans, geographically diversified across the United States. For patients with glioma who receive supplemental Medicare benefits through employer-sponsored health plans, information on the employer-paid portion of Medicare-paid benefits and patients' OOP expenses for their medical and pharmacy services were also available. The SSA death files were linked to patient enrollment data to identify patients with glioma who died, and the date of death.

The combined data set was used to study the treatment patterns, survival, and healthcare costs of patients with an incident glioma who initiated treatment with

brain surgery. A retrospective cohort study design was used with the patients stratified into 1 of 4 treatment cohorts based on the receipt of temozolomide and/or external beam radiation after their initial brain surgery.

Patient Selection and Cohorts

Patients were included if they (1) were diagnosed with malignant cancer of the brain (*ICD-9-CM*, 191.xx) on or between January 1, 2006, and December 31, 2010; (2) had undergone brain-related surgery (set as the index event) within 90 days (before or after) of the first diagnosis of 191.xx; (3) were aged ≥18 years at the index date; and (4) were continuously enrolled with medical and pharmacy benefits for 6 months before the index date.

Patients were excluded if they (1) had a diagnosis of another primary cancer (*ICD-9-CM*, 140.xx-195.xx and 200.xx-208.xx) in the 6 months before the index date; (2) had a diagnosis of secondary brain metastases (*ICD-9-CM*, 198.3) before the index date; (3) received chemotherapy or temozolomide, or had index-eligible brain surgery during the preindex period; or (4) used an off-label or nonstandard-of-care therapy as part of their first line of therapy (ie, in the 90 days after their index brain surgery), including carmustine wafer, bevacizumab, or other chemotherapy, or stereotactic radiosurgery.

The follow-up period varied for each patient and ran from the index date until a patient's date of death, disenrollment from an eligible health plan, or until March 31, 2011, whichever occurred first. Although there was no minimal postindex continuous enrollment requirement, fully adjudicated data were available through March 31, 2011, providing at least 3 months of potential data availability for all patients. To evaluate mortality as a study outcome, the analysis was limited to the subset of patients in the commercial and Medicare databases that could be linked to the SSA death data, to determine if a patient died during the study period. Patient survival was censored at the end of the follow-up.

Patients were divided into the following 4 mutually exclusive cohorts based on whether they received temozolomide and/or external beam radiation in the 90 days after the index brain surgery. The 4 cohorts included those who (1) received temozolomide only, (2) received external beam radiation only, (3) received both temozolomide plus external beam radiation, and (4) received neither temozolomide nor external beam radiation.

Study Outcomes

This study is focused on 3 types of outcomes—patterns of treatment, survival, and healthcare costs.

Treatment patterns. Among patients in 1 of the 2 temozolomide cohorts, the total duration and medication possession ratio of the first temozolomide episode is described. The end of the initial episode of temozolomide is defined as either patient death or disenrollment, or the start of a 60-day gap in temozolomide therapy. The proportion of patients restarting temozolomide therapy after a 60-day gap was also calculated.

Survival. The survival time was calculated using the date of death as obtained from the SSA; patients without a date of death were censored at the end of follow-up.

Healthcare costs. Total insurance-covered healthcare costs are reported, including both patient and plan portions of each claim for all services utilized during the study period (including those not specifically listed below). The data source includes only fully adjudicated and paid claims. The costs are reported in 3 categories of expenditures based on the location and type of healthcare resource used: inpatient, outpatient, and pharmacy. The outpatient expenditures are separated into emergency, outpatient hospital, and office visits. The pharmacy costs are classified by antiemetics, cancer therapies, neutropenia-related drugs, and pain-related drugs.

The expenditures were evaluated in 3 time periods relative to the index brain surgery—6 months before the index brain surgery, 6 months after the index brain surgery, and 12 months after the index brain surgery.

Analysis

Descriptive statistics were used for all 3 outcomes. In addition, the baseline patient clinical and demographic characteristics are described, including age, sex, health plan type, and urbanicity, as well as relevant concomitant medications and comorbid conditions.

Results

We identified 69,495 patients with an *ICD-9-CM* code of 191.xx in the MarketScan Research databases, of which 17,137 (24.7%) had brain surgery within 90 days of the 191.xx diagnosis. Of those patients, 12,143 (70.9%) were adults at the time of the index brain surgery and had 6 months of continuous medical and pharmacy coverage before the index brain surgery. An additional 4773 patients were excluded for either having another primary cancer, evidence of brain metastases, having had brain surgery, chemotherapy administration, or the use of a carmustine wafer in the 6 months of having the index brain surgery, leaving 7370 evaluable patients with a malignant brain tumor. Data regarding patient survival were available for 2484 of these patients. An additional 212 patients used a nonstandard-of-care therapy as a first-line treatment, resulting in a final study sample of 2272 patients.

The overall incidence of maligant brain tumors was 0.0056% between the years 2006 and 2010, with a range in individual years from 0.0053% to 0.0060% among

Table 1 Demographic and Clinical Characteristics

Patient characteristics[a]	All patients (N = 2272)	Patients who received temozolomide only (N = 89)	Patients who received radiation therapy only (N = 313)	Patients who received temozolomide and radiation therapy (N = 841)	Patients who did not receive temozolomide or radiation therapy (N = 1029)
Age, yrs, mean (SD)	56.9 (14.5)	55.3 (15.1)	59.8 (14.1)	56.7 (12.1)	56.3 (16.2)
Age-group					
18-34 yrs, N (%)	181 (8)	9 (10.1)	20 (6.4)	38 (4.5)	114 (11.1)
35-44 yrs, N (%)	260 (11.4)	13 (14.6)	30 (9.6)	79 (9.4)	138 (13.4)
45-54 yrs, N (%)	503 (22.1)	18 (20.2)	54 (17.3)	228 (27.1)	203 (19.7)
55-64 yrs, N (%)	648 (28.5)	23 (25.8)	73 (23.3)	303 (36)	249 (24.2)
≥65 yrs, N (%)	680 (29.9)	26 (29.2)	136 (43.5)	193 (22.9)	325 (31.6)
Female sex, N (%)	838 (36.9)	32 (36)	102 (32.6)	251 (29.8)	453 (44)
Urban residence, N (%)	1936 (85.2)	72 (80.9)	263 (84)	704 (83.7)	897 (87.2)
Health plan type					
Indemnity, N (%)	482 (21.2)	15 (16.9)	82 (26.2)	145 (17.2)	240 (23.3)
PPO, N (%)	1142 (50.3)	43 (48.3)	147 (47)	453 (53.9)	499 (48.5)
HMO, N (%)	312 (13.7)	21 (23.6)	42 (13.4)	103 (12.2)	146 (14.2)
POS, N (%)	238 (10.5)	6 (6.7)	32 (10.2)	94 (11.2)	106 (10.3)
Other/unknown, N (%)	98 (4.3)	4 (4.5)	10 (3.2)	46 (5.5)	38 (3.7)
Comorbid conditions					
Anemia, N (%)	93 (4.1)	1 (1.1)	13 (4.2)	23 (2.7)	56 (5.4)
Anxiety, N (%)	120 (5.3)	6 (6.7)	13 (4.2)	45 (5.4)	56 (5.4)
Aphasia, N (%)	69 (3)	6 (6.7)	14 (4.5)	27 (3.2)	22 (2.1)
Cerebrovascular disease/ stroke, N (%)	458 (20.2)	11 (12.4)	74 (23.6)	179 (21.3)	194 (18.9)
Cognitive deficiency, changes, or memory loss, N (%)	127 (5.6)	2 (2.2)	15 (4.8)	49 (5.8)	61 (5.9)
Depression, N (%)	123 (5.4)	6 (6.7)	16 (5.1)	36 (4.3)	65 (6.3)
Fatigue, N (%)	235 (10.3)	7 (7.9)	31 (9.9)	92 (10.9)	105 (10.2)
Headache, N (%)	502 (22.1)	12 (13.5)	54 (17.3)	212 (25.2)	224 (21.8)
Hemiparesis/hemiplegia, N (%)	50 (2.2)	1 (1.1)	5 (1.6)	21 (2.5)	23 (2.2)
Insomnia, N (%)	34 (1.5)	1 (1.1)	3 (1)	11 (1.3)	19 (1.8)
Seizures/epilepsy, N (%)	430 (18.9)	29 (32.6)	61 (19.5)	159 (18.9)	181 (17.6)
Medication use					
Antianxiety, N (%)	414 (18.2)	12 (13.5)	52 (16.6)	141 (16.8)	209 (20.3)
Anticonvulsants, N (%)	783 (34.5)	38 (42.7)	109 (34.8)	314 (37.3)	322 (31.3)
Antidepressants, N (%)	406 (17.9)	20 (22.5)	47 (15)	130 (15.5)	209 (20.3)
Antiemetics, N (%)	151 (6.6)	6 (6.7)	20 (6.4)	54 (6.4)	71 (6.9)
Corticosteroids/ glucocorticosteroids, N (%)	913 (40.2)	35 (39.3)	138 (44.1)	366 (43.5)	374 (36.3)
Pain medications (ie, NSAIDs/ COX-2 inhibitors), N (%)	304 (13.4)	12 (13.5)	46 (14.7)	112 (13.3)	134 (13)

Continued

Table 1 Demographic and Clinical Characteristics *(Continued)*

Patient characteristics[a]	All patients (N = 2272)		Patients who received temozolomide only (N = 89)		Patients who received radiation therapy only (N = 313)		Patients who received temozolomide and radiation therapy (N = 841)		Patients who did not receive temozolomide or radiation therapy (N = 1029)	
Pain medications (ie, narcotic analgesics), N (%)	593 (26.1)		16 (18)		85 (27.2)		212 (25.2)		280 (27.2)	
Sedatives/hypnotics, N (%)	218 (9.6)		8 (9)		32 (10.2)		77 (9.2)		101 (9.8)	
Survival time/death estimates[b]										
Mean survival, days (SD)	592.6	499.1	474.8	462.9	584.4	492.1	508.6	361.7	674	581.3
Median survival, days	456		331		415		426		529	
Patients alive at end of follow-up, N (%)	1177 (51.8)		43 (48.3)		128 (40.9)		269 (32)		737 (71.6)	
Mean survival, days (SD)	809.1	532.7	654	551.2	891.6	524.3	682	437.9	850.2	555.5
Median survival, days	668		447		865.5		556		748	
Observed deaths, N (%)	1095 (48.2)		46 (51.7)		185 (59.1)		572 (68)		292 (28.4)	
Mean survival, days (SD)	359.9	327.9	307.2	275.7	371.9	331.5	427	285.6	229.2	369.4
Median survival, days	272		228.5		259		373.5		72	

[a]Patient demographic characteristics are presented as of the index date. Clinical characteristics are related to the 6 months before the index.
[b]All survival time estimates measure survival time from index date. Patients who did not die during the available follow-up were included in the analysis and were censored as of the end of their enrollment.
COX indicates cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

patients in the MarketScan Research databases. The remaining 2272 patients were divided into 4 treatment cohorts based on their receipt of temozolomide and/or external beam radiation in the 90 days after their index brain surgery. The reason for this was to uncover real-world treatment patterns and to further identify a specific cohort that most likely represents a group of patients with malignant glioma receiving standard-of-care therapy.

The largest group included 1029 patients (45.3%) who did not receive temozolomide or external beam radiation in the 90 days after their index brain surgery. The second group of 841 (37%) patients received both temozolomide and radiation therapy, and is the cohort that most clearly represents the current standard-of-care therapy for patients with malignant gliomas in the United States. Smaller percentages of patients received radiation alone (13.8%) and temozolomide alone (3.9%).

Patient Characteristics

Demographic and clinical characteristics are displayed in **Table 1**. These groups were generally well balanced in terms of age, sex, geographic region, type of health plan, and the length of follow-up. The median age of the final study sample was 58 years (mean, 56.9; standard deviation, 14.5); a total of 63.1% of the patients were male, and 29.9% were aged >65 years. Corticosteroids (40.2%), anticonvulsants (34.5%), narcotic analgesics (26.1%), and anxiety medications (18.2%) were frequently used in the 6 months before the index brain surgery. Similarly, during the 6 months before the index, nearly 22.1% of patients had a claim with a diagnosis of headache, 20.2% had a diagnosis of cerebrovascular disease or stroke, and 18.9% had a diagnosis of seizures.

Survival

The median survival time was 456 days across all 2272 patients, ranging from a median of 331 days among patients who received only temozolomide to 529 days among patients who received neither temozolomide nor radiation therapy. In the cohort of patients receiving both radiation and temozolomide, the median survival was 426 days (14.2 months). Death was observed in nearly half (48.2%) of the patients, ranging from 28.4% among those who received neither temozolomide nor radiation therapy to 68% among patients who received both temozolomide and radiation.

Temozolomide Use

As shown in **Table 2**, 39.6% of patients used temozolo-

Table 2 Oral Temozolomide Use Characteristics

Characteristic	All patients (N = 2272)	Patients who received temozolomide only (N = 89)	Patients who received temozolomide and radiation therapy (N = 841)
Patients using oral TMZ in first 90 days postindex, N (%)[a]	899 (39.6)	88 (98.9)	811 (96.4)
Total duration of initial TMZ therapy, days, mean (SD)	177.9 (152.9)	155.4 (180.9)	180.3 (149.5)
TMZ prescription fills, N, mean (SD)	6.1 (5.2)	5.5 (6)	6.1 (5.1)
TMZ MPR during initial TMZ therapy, N, mean (SD)	72.7 (25.4)	73.4 (31.1)	72.6 (24.8)
Total duration of initial TMZ therapy[b]			
Patients with ≥60 days, N (%)	672 (76.5)	55 (70.5)	617 (77)
≥120 days, N (%)	486 (59.9)	37 (53.6)	449 (60.4)
≥180 days, N (%)	351 (48.1)	26 (44.1)	325 (48.4)
≥270 days, N (%)	192 (30.9)	19 (38)	173 (30.2)
≥360 days, N (%)	116 (23)	10 (25)	106 (22.8)
≥540 days, N (%)	25 (8.2)	3 (12)	22 (7.9)
60-day gap in TMZ therapy			
Patients with a 60-day gap in TMZ use, N (%)	658 (29)	51 (58)	607 (74.8)
Patients using TMZ after a 60-day gap, N (%)	144 (6.3)	15 (29.4)	129 (21.3)
Days from start of 60-day gap to restart of TMZ, mean (SD)	177 (178.52)	221 (244.98)	172 (169.65)

[a]The end of therapy with temozolomide was defined as either patient death, patient disenrollment, or the start of a 60-day gap in therapy with temozolomide. MPR is only calculated while a patient is receiving therapy.
[b]The total duration of temozolomide therapy in each time interval is only calculated for patients who are still alive and are enrolled over that same time period.
MPR indicates medication possession ratio; SD, standard deviation; TMZ, temozolomide.

mide in the 90 days after their index surgery. The duration of this therapy was, on average, 180 days for patients who received both temozolomide and radiation therapy and 155 days for patients who did not receive radiation therapy. Medication possession ratios were similar for patients who did and did not receive radiation therapy (72.6% and 73.4%, respectively). The majority of patients received temozolomide for at least 120 days (59.9%), and nearly half (48.1%) of the patients received temozolomide for at least 180 days. A total of 30.9% of the patients received temozolomide for at least 270 days.

Healthcare Costs

Table 3 lists the healthcare costs incurred by patients before and after their index brain surgery. The mean total cost over the 6 months before the index brain surgery was $11,949, ranging from $11,564 in the radiation-only cohort to $12,850 in the temozolomide-only cohort. The average total cost in the 6 months after the index surgery was markedly higher, averaging $106,896, ranging from $79,099 among patients who did not receive temozolomide or radiation to $138,767 among patients who received both temozolomide and radiation.

The total costs in the 12 months after the index surgery were higher than the costs after only 6 months, with an average cost of $131,815, and ranging from $88,827 among patients who did not receive temozolomide or radiation to $184,107 among patients who received both temozolomide and radiation. All 3 components of the total cost (ie, inpatient, oupatient, and pharmacy) showed a pattern similar to the total costs in the periods before and after the surgery.

Discussion

Although the Stupp regimen—which consists of radiotherapy and temozolomide being administered concomitantly, and then temozolomide is used after radiotherapy—has become the standard of care for newly diagnosed patients with glioblastoma, there are limited data on this patient population since the introduction of this regimen in a clinical practice setting. Using administrative claims and mortality data, this study provides data that are useful for understanding treatment patterns, survival, and the healthcare costs associated with glio-

Table 3 Healthcare Expenditures, by Index Cohort

	All patients (N = 2272)		Patients who received temozolomide only (N = 89)		Patients who received radiation therapy only (N = 313)		Patients who received temozolomide and radiation therapy (N = 841)		Patients who did not receive temozolomide or radiation therapy (N = 1029)	
Total healthcare expenditures	**Mean, $**	**SD, $**	**Mean, $**	**SD, $**	**Mean, $**	**SD, $**	**Mean, $**	**SD, $**	**Mean, $**	**SD, $**
Expenditures in the 6 months preindex surgery										
Total healthcare expenditures	11,949	17,609	12,850	15,636	11,564	17,550	12,320	19,873	11,686	15,735
Total inpatient	5368	14,133	6108	11,833	5265	13,835	6403	16,225	4490	12,424
Total outpatient	5548	7288	5873	8122	5207	6660	5005	7857	6067	6874
Emergency department	346	1299	283	579	237	649	361	1394	373	1407
Outpatient, hospital	2748	5231	2838	6020	2414	3859	2533	5799	3019	5021
Outpatient, office visits	547	463	417	471	539	444	451	396	639	499
Other outpatient	1906	3726	2335	4586	2016	4111	1661	3828	2036	3418
Total retail/mail-order pharmacy expenditures (all drugs)	1034	1578	869	1177	1093	1528	912	1242	1129	1840
Antiemetics	4	52	1	4	10	87	4	43	4	46
Cancer therapies	0	0	0	0	0	0	0	0	0	0
Neutropenia-related	3	146	0	0	0	0	0	0	7	217
Painkillers	35	253	24	76	32	141	27	231	43	302
Expenditures in the 6 months postindex surgery										
Total healthcare expenditures	106,896	97,678	111,066	108,664	111,456	84,701	138,767	76,627	79,099	107,140
Total inpatient	61,423	81,688	72,041	101,250	56,634	67,477	59,121	57,768	63,843	98,632
Total outpatient	36,109	38,660	22,895	25,786	52,063	39,975	58,860	37,701	13,804	24,174
Emergency department	525	1643	523	915	507	1239	680	1668	403	1767
Outpatient, hospital	21,602	32,426	13,488	21,868	30,963	36,302	38,047	38,144	6016	14,008
Outpatient, office visits	831	1039	1052	1937	901	1309	1211	1084	479	578
Other outpatient	13,151	22,518	7832	12,280	19,691	25,540	18,923	25,266	6905	17,490
Total retail/mail-order pharmacy expenditures (all drugs)	9364	11,323	16,130	9479	2759	3840	20,786	9590	1452	3046
Antiemetics	431	1110	549	862	400	1266	905	1453	44	335
Cancer therapies	7057	9757	13,555	7710	586	2100	17,204	8116	170	1396
Neutropenia-related	38	532	19	179	31	411	71	747	16	337
Painkillers	43	161	36	145	52	168	42	125	40	185
Expenditures in the 12 months postindex surgery										
Total healthcare expenditures	131,815	121,379	134,512	115,938	131,869	101,065	184,107	112,929	88,827	117,423
Total inpatient	68,645	90,003	74,465	102,251	63,385	73,947	71,487	73,371	67,419	104,511
Total outpatient	49,212	58,986	35,427	43,706	63,124	48,980	82,750	68,286	18,763	32,572
Emergency department	732	1943	815	1421	723	1583	965	2032	538	1988
Outpatient, hospital	29,128	48,770	18,110	28,083	38,082	45,189	52,060	64,125	8615	17,910
Outpatient, office visits	1306	1567	1547	2564	1363	1724	1883	1782	796	911
Other outpatient	18,046	30,249	14,955	29,688	22,956	27,190	27,841	36,118	8814	21,993

Continued

Table 3 Healthcare Expenditures, by Index Cohort *(Continued)*

	All patients (N = 2272)		Patients who received temozolomide only (N = 89)		Patients who received radiation therapy only (N = 313)		Patients who received temozolomide and radiation therapy (N = 841)		Patients who did not receive temozolomide or radiation therapy (N = 1029)	
Total healthcare expenditures	**Mean, $**	**SD, $**	**Mean, $**	**SD, $**	**Mean, $**	**SD, $**	**Mean, $**	**SD, $**	**Mean, $**	**SD, $**
Total retail/mail-order pharmacy expenditures (all drugs)	13,957	17,723	24,621	19,657	5360	8504	29,870	17,173	2645	5502
Antiemetics	575	1495	715	1158	578	1892	1190	1911	59	421
Cancer therapies	10,059	14,915	20,349	14,691	1529	5482	23,962	14,533	402	2905
Neutropenia-related	96	1296	249	1694	84	1312	181	1856	16	337
Painkillers	78	380	49	212	87	316	89	424	68	371

SD indicates standard deviation.

blastoma as observed in a large, representative commercially insured US population.

The current *ICD-9-CM* classification system does not clearly discriminate patients by histopathology, and patients with a diagnosis code of 191.xx can represent a heterogeneous group of tumor types. Although this is a limitation of this current analysis, malignant gliomas make up the overwhelming majority of malignant brain tumors in adults, and the contribution of other rare tumors is likely inconsequential.[10] One group that may be coded as 191.xx may include lower-grade gliomas, which eventually progress into higher-grade tumors.

To purify our sample, we determined the treatments that patients received to better understand their potential tumor makeup. We created 4 mutually exclusive categories based on the patients' exposure to radiation and/or temozolomide therapy. Remarkably, more than 40% of patients received neither of these therapies. The relatively high median survival in this group suggests that many of these patients might have had lower-grade histologies, for whom upfront radiation and/or temozolomide are not clearly standard-of-care therapies.[11]

It is possible that this cohort includes elderly or poorly performing patients in whom a decision was made not to pursue active treatment; however, these patients did not appear substantively different from the other treatment cohorts, particularly in terms of the distribution of age-groups. Therefore, it is more likely that, in this analysis, less-aggressive treatment is an indicator of lower-grade gliomas, where such less-aggressive treatment is clinically reasonable.

The preindex healthcare utilization was similar across the 4 cohorts; therefore, the difference in treatment cohort costs does not appear to be a result of the background comorbid burden, or the patient's clinical profile. Furthermore, we sought to characterize a cohort of patients that most likely represent patients with newly diagnosed glioblastoma based on the type of treatments that they received. For that purpose, we defined the standard of care based on the Stupp regimen,[3] and after applying exhaustive inclusion and exclusion criteria, we were able to identify 841 patients who received radiation plus temozolomide therapy. Although a small portion of these patients could have anaplastic gliomas, given the emerging treatment patterns in tertiary care centers,[12] we believe that our cohort of 841 patients receiving temozolomide plus radiation are patients with glioblastoma. This is because anaplastic gliomas are rare compared with glioblastoma, and the median survival in this cohort (of 426 days, or 14.2 months) fits closely with the findings reported with the Stupp regimen for glioblastoma (14.6 months).[3]

The role of temozolomide for anaplastic gliomas in the upfront setting, however, remains controversial. Anaplastic gliomas, which are World Health Organization grade 3 tumors, make up less than 50% of all malignant gliomas; they are a heterogenous group of tumors in terms of their histology, molecular markers, treatment, and survival.[13] Because of the rarity of these tumors, few large phase 3 clinical trials have been conducted to inform optimal therapies.

In the United States, the treatment of these tumors is increasingly extrapolated from studies done on patients with glioblastoma. A recently published large phase 3 trial has confirmed a role of chemotherapy for 1p/19q codeleted anaplastic oligodendrogliomas, but because this study was conceived more than 20 years ago, it investigated procarbazine, lomustine, and vincristine therapy rather than temozolomide therapy.[14] An ongoing large phase 3 trial from the Radiation Therapy Oncology Group (RTOG) is addressing the role of temozolomide in anaplastic gliomas (clinicaltrials.gov identifiers NCT01847235 and NCT00033280); but as of now, there

are no prospective data that demonstrate efficacy of temozolomide in this population. Given the costs and the lack of evidence, one may consider enrolling such patients in active RTOG trials that are aiming to properly and systematically address the question of temozolomide's efficacy in anaplastic gliomas.

Not surprising, our study shows that healthcare utilization and costs increase after patients with malignant glioma have surgery. In our analysis, in the 1 year after surgery in the 841 patients with presumed glioblastoma who received radiation and temozolomide therapy, the total healthcare expenditure was $184,107. This cost is substantially higher than in the study by Kutikova and colleagues, which did not report any inclusion of temozolomide data, but that estimated the 1-year healthcare costs to be less than $80,000.[9]

In this current analysis, the total costs for patients who received both temozolomide and external beam radiation were 1.8 times greater over 6 months than for patients who received neither, and 2.1 times greater over 12 months. After 6 months, the cost for patients who did not receive temozolomide or external beam radiation returned to their presurgery levels; the average 6-month preindex cost was $11,868; the average cost for months 7 to 12 postindex were $9728.

Our descriptive analysis did not identify predictors of healthcare costs, treatment patterns, or patient survival. There are several known predictors of improved survival, such as age, performance status, and tumor O6-methylguanine-DNA methyltransferase (MGMT) methylation.[15] Patients managed with methylation of the MGMT promoter have shown improved survival, but broad implementation of testing remains impractical,[16] warranting further research and potential promise for treatment prognosis, at least among some subgroups of patients.[17]

As the US population ages, we expect a rise in the incidence of glioblastoma, and the burden on third-party payers may change substantially over the next few decades.[18] The Stupp regimen excluded patients aged >70 years, and there is controversy regarding the role of adjuvant chemotherapy in older patients. A recent phase 3 study showed that temozolomide therapy alone in highly functioning elderly patients is tolerable and is noninferior to radiation therapy alone.[19] Another study comparing radiation with temozolomide to radiation alone demonstrated a marginal improvement in survival with chemotherapy,[20] and even poorly functioning elderly patients seem to derive some benefit from temozolomide therapy.[21]

Limitations

This study had several limitations. In addition to the previously noted limitation regarding the specificity of *ICD-9-CM* coding, there are additional limitations inherent in the data source used in this analysis. Administrative claims data lack information on disease severity or staging.

Similarly, there is limited information on patient or provider characteristics that may influence medical decision-making. This also limits our ability to differentiate the treatment cohorts or to potentially predict or explain the reasons for administering temozolomide and/or external beam radiation therapy.

Although it is necessary to describe the baseline characteristics and to establish the incident event, the preindex continuous enrollment requirement may bias the study sample toward patients with stable health insurance who may be healthier than patients with intermittent health insurance, or the uninsured.

The 4 cohorts were defined based on treatments received in the 90 days after the index surgery event, because this corresponded with a clinically reasonable time period to initiate either temozolomide or external beam radiation therapy. Patients in any of these cohorts could potentially receive (or initiate) temozolomide therapy outside of this 90-day time period.

Conclusion

Based on our analysis, the addition of temozolomide to the treatment regimens for glioblastoma increases the cost of care, and the use of temozolomide potentially indicates greater disease severity. Although survival in this clinical practice setting–based analysis is similar to the survival reported in clinical trials, further cost-effectiveness and quality-of-life analyses will be critical to better understanding the value of temozolomide therapy in treating this patient population, particularly because of the availability of generic temozolomide. ■

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Author Disclosure Statement

Dr Ray is an employee of and has stocks in AbbVie; Dr Bonafede reported no conflicts of interest; Dr Mohile is a consultant to Truven Health Analytics and to Abbott Laboratories, and is on the speaker's bureau of NovoTTF.

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STAKEHOLDER PERSPECTIVE

Treatment Decisions in the Management of Malignant Gliomas

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PAYERS: Glioblastoma multiforme (GBM) is an extremely aggressive malignant brain tumor, accounting for more than 50% of all functional brain tumor cases in humans.[1] Before 2005, the standard of care for treatment was surgery, radiation therapy, and chemotherapy. The standard of care changed after the study by Stupp and colleagues that demonstrated an improvement in median survival of 14.6 months for patients treated with radiotherapy plus temozolomide compared with 12.1 months with radiotherapy alone.[2]

In the current article by Ray and colleagues, the authors used large databases to describe the treatment patterns, survival, and healthcare costs associated with the new standard of care for patients with GBM. They conclude, as may be expected, that the costs are higher in patients receiving temozolomide, and their analysis from real-world data on survival closely mirrors that seen in clinical trials.

What should be of interest to payers to build on this study are additional analyses to determine which subgroups may respond better to treatment based on a patient's baseline health status and age. In particular, the *O6-methylguanine-DNA methyltransferase* gene in patients with GBM has been shown to be of potential use for its prognostic and predictive values in targeting specific patients who may respond better to treatment.[3] Although the medical community believes that this test is still not ready for routine use in clinical practice, watching its development and application in actual practice may help with treatment decisions.[4]

PATIENTS/PROVIDERS: As with any therapy for cancer, quality of life will continue to play a critical role in treatment decisions related to patients with GBM, by patients, providers, as well as payers. ■

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