Original Contribution

Economics of Malignant Gliomas: A Critical Review

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Abstract

Purpose: Approximately 18,500 persons are diagnosed with malignant glioma in the United States annually. Few studies have investigated the comprehensive economic costs. We reviewed the literature to examine costs to patients with malignant glioma and their families, payers, and society.

Methods: A total of 18 fully extracted studies were included. Data were collected on direct and indirect costs, and cost estimates were converted to US dollars using the conversion rate calculated from the study's publication date, and updated to 2011 values after adjustment for inflation. A standardized data abstraction form was used. Data were extracted by one reviewer and checked by another.

Results: Before approval of effective chemotherapeutic agents for malignant gliomas, estimated total direct medical costs in the United States for surgery and radiation therapy per patient ranged from $50,600 to $92,700. The addition of temozolomide (TMZ) and bevacizumab to glioblastoma treatment regimens has resulted in increased overall costs for glioma care. Although health care costs are now less front-loaded, they have increased over the course of illness. Analysis using a willingness-to-pay threshold of $50,000 per quality-adjusted life-year suggests that the benefits of TMZ fall on the edge of acceptable therapies. Furthermore, indirect medical costs, such as productivity losses, are not trivial.

Conclusion: With increased chemotherapy use for malignant glioma, the paradigm for treatment and associated out-of-pocket and total medical costs continue to evolve. Larger out-of-pocket costs may influence the choice of chemotherapeutic agents, the economic implications of which should be evaluated prospectively.

Introduction

In 2012, approximately 1.64 million persons were diagnosed with cancer in the United States.[1] Although malignant brain tumors account for only 1.4% of the total cancer cases,[1] they cause permanent injury to the brain, are commonly resistant to most treatments, and result in disproportionately high morbidity.[2] Current standard treatment for glioblastoma multiforme (GBM) is radiation therapy (RT) plus temozolomide (TMZ), followed by 6 to 12 months of maintenance TMZ. No standard exists for grade 3 gliomas, but treatment includes the above regimen, chemotherapy alone, or RT alone. At progression, many patients are treated with bevacizumab if they are not eligible for a clinical trial. Patients age 65 years and older receive full-dose RT plus TMZ, unless they are frail or do not tolerate RT; for those patients, short-course RT may be used, or RT may be omitted. Gliomas account for 45% to 50% of all malignant tumors of the CNS.[23]The majority of gliomas arise from astrocytes and are classified as low-grade astrocytomas, anaplastic astrocytomas, or GBM; the latter making up more than half of all cases. Median patient survival after GBM diagnosis is less than 15 months, despite aggressive standard treatment involving tumor resection, 6 weeks of radiation with concomitant TMZ, and six cycles of adjuvant TMZ. Bevacizumab is currently indicated for the treatment of recurrent GBM, with a median overall survival of approximately 9 months.[3-5]

The SEER Program database reports the 5-year relative survival rate for GBM as 3.3%, but current data suggest an approximately 10% survival for patients treated with RT at 2 years and 27% for patients treated with RT and TMZ.[6,7]

Despite the high morbidity and mortality associated with malignant glioma, little attention has been paid in the United States to its economic costs. Reviews in Europe have focused on treatment costs associated with TMZ[8,9] and carmustine implants.[10] Direct medical costs have been reported in several large insurance claims database studies, but indirect costs associated with premature death or years of productive life lost need consideration. Low-grade and anaplastic gliomas, which affect adults between ages 20 and 55, exert the greatest economic impact; the overall economic impact of GBMs, in comparison, is less, as median at diagnosis is 55 years. However, with many people working beyond age 65, lost productivity for geriatric patients is becoming increasingly important.

In an age of limited resources and soaring health care costs, economic assessments of malignant gliomas, with their frequent

occurrence in younger and middle-aged individuals, is particularly important. Herein, we review and summarize the literature relative to the direct and indirect costs of malignant gliomas for patients and their families, payers, and society.

Methods

We systematically searched MEDLINE, PubMed, EMBASE, and the Cochrane Library from January 1996 through March 2011. Abstracts from recent scientific meetings and reference lists of relevant reviews were hand-searched to identify additional studies. A standardized data extraction form was used, which allowed for input of information from different trials and for subgroup analysis: type of study, participants, interventions, outcomes, decision to include or exclude a study, and organizational aspects (author, year, country of origin, publication type). It also allowed for the classification or grouping of several studies with common features (eg, study quality, protocol of intervention) and included a section on reasons for exclusion of a study from review, such as methods used by the included studies, patient characteristics (eg, age), and outcomes. Studies that failed one of the checks were discarded. Only four studies fell into this category. "AND" narrowed our search by ensuring that all of our terms were in the article of interest. "OR" broadened our search to include results that contained either of the terms in the article of interest and was useful for linking synonyms. Additionally, the Physician Data Query clinical trials database and the proceedings of the 1997 to 2010 ASCO Annual Meetings were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials. The quality of randomized clinical trials and nonrandomized controlled studies was assessed using standard checklists.[11] We used the following search terms: economics, costs, cost-benefit analysis, cost effectiveness, cost of illness, insurance coverage/statistics and numerical data, brain cancer, and glioma. Content experts provided additional potential studies not identified by the database searches. Three investigators (K.F., J.R., and J.M.M.) independently reviewed all identified publications for inclusion using predetermined criteria. Disagreements were resolved by an independent adjudicator. No language restrictions were applied. Studies published in a language other than English were translated before consideration for inclusion. Included studies were those that looked at direct and indirect medical cost reports: direct costs are costs paid for medical goods and services related to the diagnosis and treatment of a disease; indirect costs are the estimated economic losses associated with cancer-related employment drop-out (short or long-term), decrease in productivity, lost salary, and early retirement pensions, as well as losses due to travel, food, out-of-pocket expenditures for medical care, and costs related to loss of income and expenses incurred by family members, spouses, and caregivers as a consequence of a cancer diagnosis for an individual patient. Cost estimates were converted to US dollars using the conversion rate calculated from the study's publication date and were updated to 2012 values after adjustment for inflation based on the date of publication. The Consumer Price Index for all goods and services was used for the adjustment. Inflation rates were obtained from the United States Department of Labor, Bureau of Labor Statistics Web site.

Results

Our search yielded 32 studies; 18 systematic reviews or meta-analyses met our criteria and were fully reviewed. The 10 studies with the best fit appear in Table 1; others are discussed in the text below.

Direct Medical Costs

In 2004, Chang et al[6] examined direct costs associated with seven types of cancer in the United States after reviewing insurance claims of three million Americans between 1998 and 2000. Brain cancer ranked fourth in mean total direct medical costs per month at $8,478, based on 652 patients. Services, specifically RT ($877 per month; standard deviation [SD], $1,913) and surgery ($486 per month; SD, $2,243) contributed most to the direct costs of brain cancer; mean cost of outpatient chemotherapy dispensing was only $8 per month (SD, $51; Table 1).

Silverstein et al[12] investigated the direct costs of care for patients with anaplastic astrocytomas (AA) and GBM. This study included 64 patients diagnosed between 1987 and 1992 at the Mayo Clinic, and estimated mean and median total cost of direct medical services to be $99,253 and $91,368, respectively. Radiotherapy (RT) costs were the most expensive ($14,050), followed by imaging ($14,238).[10,12] Three quarters of the charges were incurred in the initial treatment period (median of 116 days). Direct costs reached a plateau after 1 year, likely as a result of low survival rates (median survival, 323 days). Polinsky et al[13] estimated the average costs for 29 patients undergoing standard craniotomy ($16,292) and 15 patients undergoing stereotactic craniotomy ($12,178) in Ann Arbor, MI. Cost was calculated by addition of hospital charges. Studies in Nova Scotia[13] and the United Kingdom[14] evaluated the costs of brain tumors outside of the United States.

Blomqvist et al[15] reported direct costs of care for brain tumors in Sweden in 1996 as $68.0 million per million population (estimated average direct costs = $6,445); of these costs, 71% were for short-term hospital care, 19% for long-term hospital-based home care, and 3% for ambulatory care/drugs. Johannesen et al[16] collected data on primary treatment costs for patients with glioblastoma with three treatment options in Oslo, Norway from 1985 to 1999. They estimated an average cost of $32,764 for 58 patients treated with RT, $29,596 for 75 patients treated with accelerated RT, and $23.408 for 41 patients treated with intracavitary brachytherapy.

Indirect Costs

The National Brain Tumor Foundation assessed the financial impact of brain tumors using an online survey from 277 patients and 224 caregivers.[17] Ninety-one percent of respondents had medical insurance. Despite being out of active treatment, 34% of respon-

Table 1. Estimated Direct Costs of Brain Cancer for the Most Frequently Evaluated Components of Total Direct Costs

Study (Country)	Data Source	Sample Size	Study Period	Cost Calculation Methods	Costs of Surgery, RT, Outpatient Drugs*	Overall Cost*
Joahnnesen et al[17] (Norway)†	National data sources	171	1985-1999	Estimated primary treatment costs for patients with glioblastoma with three treatment options	Surgery: N/A; RT: $25,618 ($32,665.73); outpatient drugs: N/A	Total average cost per patient: $25,618 ($32,665.73) for RT, $23,442 ($29,891.09) for accelerated RT, $14,534 ($18,532.43) for intracavitary brachytherapy
Silverstein[12] (United States)†	Cost data taken from Rochester Epidemiology Project and Olmstead County Utilization Study; clinical data from chart reviews at the Mayo Clinic	64	1987-1992	An all-payer perspective was used. Medical charges were used to estimate direct medical costs of treatment.	Surgery: $7,514 ($10,985.67); RT: $9,610 ($14,050); outpatient drugs: N/A	Total cost per patient: $67,887 ($99,252.61)
Latif[15] (United Kingdom)†	Patient data from the Department of Clinical Neurosciences at Western General Hospital, Edinburgh	236	1989-1995	Median cost per patient was calculated, followed by median cost of each week survival. Amounts calculated using unit costing according to NHS National Costing Project	Surgery: N/A; RT: $28,494 ($40,099.97); outpatient drugs: N/A	N/A
Mehta[38] (United States)†	Computerized billing forms for patients treated at University of Wisconsin	635	1989-1994	Costing analysis for estimated average costs	Surgery: $13,729-$27,523 for those receiving radiation and surgery ($19,621.95 to $39,336.80); RT: $16,250 ($23,225.05); outpatient drugs: N/A	Average cost per week of survival: $310 ($443.06) for RT, $524 ($748.92) for resection plus radiation, and $270 ($385.89) for radiosurgery plus radiation
Polinsky et al[13] (United States)†	Costs of patients treated in a hospital in Ann Arbor, MI	29	1990-1995	Average costs calculated for patients undergoing craniotomy or stereotactic craniotomy Cost was calculated by addition of hospital charges	Surgery: N/A; RT: N/A; outpatient drugs: N/A	Average costs for craniotomy: $11,365 ($16,243); stereotactic craniotomy: $8,495 ($12,141.34)
Blomqvist et al[16,45] (Sweden)†	National data sources	Swedish population	1996	Nationwide costs of ambulatory, in hospital, long term and palliative/ terminal care, drug consumption, temporary and long term morbidity	Surgery: N/A; RT: N/A; outpatient drugs: N/A	Average direct costs of care: $4,599 ($6,445); 71% of the costs, were for short-term hospital care, 19% for long-term hospital-based home care‡
Mendez[14] (Canada)†	Utilization and clinical data gathered from records of patients treated at Queen Elizabeth II Health Sciences Centre in Nova Scotia	61	1996-1998	Unit cost data and patient-specific utilization from hospital records	Surgery: $7,957 ($10,306.45); RT combined with surgery: $12,175 ($15,769.89); outpatient drugs: $663 ($858.76)	Average total cost per patient: $11,446 ($14,580); 25% were RT costs, 16% were surgery costs, 7% were chemotherapy costs
Chang et al[6] (United States)	Data source: Insurance claims of 3 million Americans	652	1998-2000	Cancer costs (seven types of cancer) in a retrospective study	Surgery: $365 ($486) per month, SD, $1,684 ($2,243); RT: $658 ($877) per month, SD, $1436 ($1,913); outpatient drugs: $6 ($8) per month, SD, $38 ($51)	Mean total direct medical costs per patient per month $6,364 ($8,478)
Kutikova[39] (United States)	Data source: MarketScan commercial claims and encounters and Medicare Supplemental and Medicare supplemental and Coordination of Benefits databases	653	1998-2000	Resource utilization and direct costs were summarized as monthly means and the total amount over the follow-up period	Surgery: N/A; RT: $645 ($713.59) per month outpatient; outpatient drugs: $249 ($275.48) per month	Total cost per patient $49,242 ($54,478.69)
Mabasa[22] (Canada)	Prospective patient cost data; medical records for those in treatment in Canada	41	2001-2002	Overall survival, duration of therapy, drug cost, labor and supplies, and successive or prior chemotherapy	Surgery: N/A; RT: N/A; outpatient drugs: TMZ $7,430 ($8,454.28); lomustine $98 ($111.51)	Total cost per life-year gained: $32,247 ($36,692.48) to $162,186 ($184,544.50)

Abbreviations: N/A, not applicable; NHS, National Health Service; RT, radiotherapy; SD, standard deviation; TMZ, temozolomide

* Values in parentheses represent 2012 inflation-adjusted costs in dollars.

† Studies were conducted before TMZ received FDA marketing approval in the United States (August 1999), Medicines Control Agency approval in the United Kingdom (January 1999), and Health Canada approval (1999).

‡ We estimated the prevalence/incidence and per-person cost of brain cancer in 1997 using data from data provided by Blumqvst and the Swedish government.[45]

dents and 54% of caregivers reported out-of-pocket costs of more than $271 each month. For 5% of respondents and 27.2% of caregivers, out-of-pocket costs were more than $1,900 each month. In all categories assessed, caregiver out-of-pocket expenses were greater than those of the patients. Medications accounted for the greatest out-of-pocket medical cost, whereas meals, transportation to treatment, telephone bills, housing, and consumer goods accounted for the greatest nonmedical costs.[17]

The National Brain Tumor Foundation 2006 survey found that 91% of patients with brain tumors were employed prediagnosis versus 33% postdiagnosis.[17] For caregivers, 16% discontinued employment, and 62% decreased their hours or took time off. Decreased household income was reported by 48% of respondents, and families reported decreased spending overall.[17]

Blomqvist et al[15] estimated that the total indirect costs (sick leave, early retirement, and mortality) amounted to $197.7 million for the Swedish population ($22.5 million per million). These indirect costs accounted for the vast majority (74%) of the total cost of illness ($101,058 per patient) in 1996. Mortality for patients younger than 65 years accounted for 73.1% of the indirect costs. Early retirement pensions cost $378.4 million in lost production (19.2% of indirect costs), and temporary morbidity (sickness leave) cost $15.5 million (7.7% of indirect costs).[15]

Chemotherapeutic Treatment and Cost Effectiveness

The carmustine wafer received US Food and Drug Administration (FDA) approval in September 1996 and February 2003 for recurrent malignant gliomas and newly diagnosed malignant gliomas, respectively. Rogers et al performed a cost analysis of carmustine wafers, estimating a cost effectiveness of $115,458 per quality-adjusted life-year (QALY); $50,000 per QALY is often considered the upper limit of cost-effectiveness, although in this trial $30,000 was used.[17,18]

Three years after initial FDA approval of the carmustine wafer, TMZ, an oral chemotherapeutic agent, was approved by the FDA for recurrent AA and in 2005 for newly diagnosed GBM. TMZ is now part of the standard of care for patients with newly diagnosed GBM. In 2001, Dinnes et al published a report on the cost effectiveness of TMZ in recurrent malignant glioma, highlighting increase in progression-free survival (PFS), but not overall survival[19] (Table 2).

Wasserfallen et al found mean treatment costs for 49 patients treated with TMZ for first or second relapse after RT to be $31,274, accounting for an average of 61% of the total costs of care, with the acquisition cost of TMZ being 76% of the total drug cost.[20] The mean cost associated with first relapse was $8,131, and the total cost of TMZ treatment (mean of 5.4 cycles) was $17,847. From the completion of TMZ treatment to relapse, progression, or death, the average cost per month was $4,389. Median post-treatment survival was 3.6 months, and mean cost per patient was $15,804. After relapse, 13 patients started continuous TMZ (42 days on and 14 days off) for a cost of $4,696. In seven patients, TMZ was continued with other drugs for a cost of $5,942, and in six patients TMZ was discontinued and other drugs were given, for a cost of $5,114. Mean survival in patients who received continuous TMZ alone (12.6 months) or TMZ with other drugs (12.0 months) was longer than for patients who received no treatment (8.2 months) or other drugs only (6.7 months). Because continuous TMZ was administered to patients with better prognoses, these patients had longer survival. On the basis of a 95% CI and the calculation methods used by the authors, the average cost per life-year gained ranged from $39,012 (2011 inflation-adjusted cost: $45,822.55) to $52,054 ($61,140.20). The cost per QALY ranged from $55,731.88 ($65,460.56) to $72,251 ($84,863.24). The authors felt these were acceptable costs even though they exceed the generally accepted cost-effectiveness threshold[20] (Table 2). Wasserfeld et al also reported that use of TMZ as concomitant and adjuvant treatment until disease recurrence represents an eight-fold increase in cost compared with standard RT alone.

In Canada, Mabasa et al compared cost of drug therapy (lomustine or TMZ) in patients with a diagnosis of AA and GBM who experienced a first relapse and had not received other drugs as part of a regimen or as adjuvant therapy.[21] (Table 1) On the basis of TMZ's higher cost and lack of additional clinical benefit, lomustine was found to be a more cost-effective treatment strategy. However, the authors noted that in British Columbia, TMZ was the treatment of choice for recurrent malignant gliomas because of its clinically perceived benefit relative to the health-related quality of life of those patients and its safety record.[21]

On the basis of the cost-effectiveness analysis of these and other similar studies, the National Institute for Clinical Excellence (NICE) in the United Kingdom recommended TMZ treatment consideration for patients for whom first-line chemotherapy with other agents had failed and whose life expectancy exceeded 12 weeks at treatment initiation. The NICE guidance estimates the cost per progression-free week to be $1,955 for GBM and $1,368 for AA.[22] The cost per life-year gained was estimated at $78,185 for both GBM and AA.[3]

Discussion

The available data suggest that cost of care is significant in the treatment of patients with malignant gliomas. Both carmustine wafers and TMZ have contributed substantially to the increased per-patient costs for brain tumor treatment, and further increase is anticipated with bevacizumab approval. For newly diagnosed GBM, new extended-dose trials for TMZ showed a benefit over procarbazine, but insufficient to receive approval in the United States.[23-25] Preliminary data highlight potential survival benefits in a subset of glioblastoma patients with methylated methylguanine-methyltransferase (*MGMT*) gene promoters[26]; the MGMT repair enzyme has the ability to revert the DNA damage induced by alkylating agents like TMZ, thus silencing of the gene increases the effectiveness of TMZ therapy.

In 2009, the FDA granted accelerated approval for bevacizumab as monotherapy for glioblastoma with progressive disease after prior therapy.[27-29] Administration of bevacizumab in combination with irinotecan or other chemotherapeutic agents for recurrent GBM has resulted in monthly cost far greater than that of TMZ. For patients treated with bevacizumab alone on a 10 mg/kg dose biweekly, the cost is approximately $10,000 to $20,000 per

Table 2. Cost Effectiveness of Chemotherapy for Patients With Primary Brain Tumors

Study (Country)	Study Type	Study Methods	Population	Therapy	Purpose	Cost Effectiveness*†
Dinnes et al 2001[20] (United Kingdom)	Literature review augmented by cost-effectiveness and cost-utility analyses	Searched Cochrane, MEDLINE, EMBASE, CANCERLIT, Toxline, ISI Web of Science, BIOSIS and PreMedline using generic and trade drug names. Compared cost effectiveness and cost utility of TMZ to best alternative care. Estimated direct costs for incremental cost of TMZ administration/follow-up. Performed sensitivity analysis	Patients with GBM and AA who were included in seven published effectiveness studies	TMZ	To review the cost effectiveness of TMZ for primary malignant brain tumors (AA and GBM)	$61,370 ($78,184) per QALY for recurrent GBM; $57,960 ($88,116) per QALY for recurrent AA
NICE 2004[23] (United Kingdom)‡	Technology assessment with cost-effectiveness analysis	Technology assessment critically appraised trails, extracted data, and conducted a narrative synthesis of the evidence. Random effects model used where possible; Markov model assessed the cost utility of the interventions. Sensitivity analysis was performed	Simulated cohort of 1,000 UK patients with mean age of 55 years. Modeled over 5 years	Carmustine wafers (BCNU-W) plus TMZ	To assess the clinical and cost effectiveness of adjuvant BCNU-W and concomitant TMZ, compared with surgery and radiotherapy	ICER per life-year gained with TMZ against procarbazine is $62,447 ($75,833); $65,366 ($74,525) per QALY for recurrent malignant gliomas
Wasserfallen et al 2004[40] (Switzerland)	Prospective cost analysis as part of a Phase II trial	Cost comparison of the addition of TMZ and radiotherapy treatment to the cost of radiotherapy alone. cost analysis based on incurred resource use	46 patients ages 24-70 years	TMZ	To review the cost effectiveness of TMZ for primary malignant brain tumors	Median $27,684 per year of survival; approximately $50,000 ($60,717.84) per 4 months of life gained
Wasserfallen et al 2005[21] (Switzerland)	Cost assessment; prospective RCT of TMZ	Total cost based on incurred resource utilization (costs/prices of personnel, drugs, imaging, laboratory tests and hospitalization day rates) were calculated from chart review and payer data. Cost effectiveness and cost-utility ratios were computed. Observation period 1: duration of TMZ treatment for first recurrence; observation period 2: end of TMZ treatment until death	49 patients with recurrent or progressive gliomas, ages 23-79 years	TMZ	Compare true total costs of treating patients with GBM at first recurrence	Overall monthly costs of care varied between $3,317 ($,3895.80) and $4,389 ($5,155.15); $39,012 ($45,822.55) to $52,054 ($61,140.20) per life-year gained; $55,731.88 ($65,460.56) to $72,251 ($84,863.24) per QALY
Martikainen et al 2005[41] (Finland)‡	Cost modeling simulation	Cost-effectiveness analysis of TMZ and PCV using a decision-modeling approach	Systematic review of five studies	TMZ	Compare cost effectiveness of TMZ with PCV in patients; estimate different societal willingness-to-pay levels	$39,635 ($46,553.70) per life-year gained for recurrent GBM
Lamers et al 2008[42] (Europe and Canada)	Prospective RCT; cost-effectiveness analysis	Cost-effectiveness analysis	219 patients with glioblastoma, ages 18-70 years, from institutions in Austria, Switzerland, Germany, Canada, the Netherlands	TMZ	To compare the cost effectiveness of concomitant and adjuvant TMZ to radiotherapy alone	ICER = $54,558 ($58,128.45) per life-year gained for newly diagnosed GBM when Dutch unit costs were used; $63,940 ($70,488.80) for Swiss unit costs; and $50,917 ($56,132.02) for Canadian unit costs
Rogers et al 2008[19] (United Kingdom)	Decision analytic modeling	Markov cost-utility model; probability cost obtained from published literature and expert opinion. Considered willingness to pay. Sensitivity analysis was conducted.	Two simulated treatment cohorts were modeled for those in the UK with a new diagnosis of glioma and a mean age of 55 years	BCNU-W	Assess cost-effectiveness of BCNU-W as an adjunct to surgery followed by radiotherapy compared with surgery and radiotherapy. Inform policy-making by the NICE technology appraisal program.	$108,040.80 ($115,110.78) per QALY for newly diagnosed malignant gliomas

Abbreviation: AA, anaplastic astrocytoma; BCNU-W, bis-chloroethylnitrosourea (carmustine) wafers; GBM, glioblastoma multiforme; NICE, National Institute for Clinical Excellence; PCV, procarbazine, cyclophosphamide, and vincristine; QALY, quality-adjusted life-year; RCT, randomized clinical trial; TMZ, temozolomide.

* Values in parentheses represent 2011 inflation-adjusted costs in dollars.

† Cost effectiveness is measured either by cost per life-year gained or cost per QALY, the latter taking into account both the quantity and quality of incremental life-years gained.

‡ Includes findings from some studies that are reflected in this table.

month (as calculated by Epocrates; Athenahealth, Princeton, NJ) or $120,000 to $240,000 per year for a patient weighing 70 kg, excluding other combination chemotherapies, other associated costs of infusion, loss of work, and other indirect costs such as parking. Patients can receive this drug for up to 12 to 24 months, with resultant increase in health-related costs.[30] Continued use of bevacizumab with RT and TMZ, despite lack of current efficacy data, contributes additional costs.

In March 2009, intravenous TMZ received approval from the FDA and European Commission for the same indications as those of its oral formulation, and in April 2009, the Centers for Medicare and Medicaid Services granted a preliminary Healthcare Common Procedure Coding System code for TMZ 1 mg injection.[31] The costs for patients treated with intravenous TMZ might be similar to those of bevacizumab, especially if given in combination with RT, but as noted could have a higher coverage rate than oral TMZ as a result of incidental costs noted above. In light of findings from the ASCO reports of AVAglio and RTOG Study I, it is unlikely that bevacizumab will be used for upfront treatment of GBM, but it may continue to be used at progression only.[32] Intravenous TMZ use will likely be restricted to a select group of patients, such as those unable to swallow the capsules.

Economic analyses provide useful information for decision making; the cost-effectiveness ratio provides a measure of the efficiency of each intervention being considered in producing an additional QALY, thereby allowing for comparison of alternative approaches or therapies. Economists tend to agree that indirect cost of illness is essential to consider when addressing cost of malignant brain tumors. However, economic analytic methods have not yet been perfected, particularly with regard to how certain indirect costs should be categorized and calculated. The US Public Health Service (PHS) has articulated a standard method for undertaking cost-effectiveness analysis, recommending calculation of the incremental cost-effectiveness ratio (ICER) and use QALY, which reflects both quantity and quality of life.[32a,32b] The Public Health Service Task Force also recommends that one consider how an intervention affects all costs relative to a disease, including costs that patients incur and overall health care expenditures.[33] Lost wages and productivity are implicitly included in this perspective. However, Nyman[34] identifies issues in the construction of QALYs and between the measurement of productivity costs and the societal perspective.

Concerns exist among economists about including a lost productivity measure in an ICER calculation because the measure may appear in both the numerator and denominator. Patients may include a value for their lost productivity when valuing their quality of life (denominator), and the economist may include a lost productivity measure in the cost (numerator). Productivity loss measures are further complicated by the availability of two accepted calculation methods: human capital and friction capital. These methods are likely to produce different valuation because the former considers lost earnings of the worker from the date of diagnosis to potential date of retirement; the latter assumes that the position will be filled in a certain period of time and that productivity will return to normal over a period of time, resulting in lower costs. [35,36]

Limitations

The cost data were derived from a variety of sources, countries, and health care systems, making comparisons and generalizability difficult. The studies also presented costs that may have been based on charges, which, as Finkler notes, do not necessarily reflect true economic costs.[37]

Summary

As treatment paradigms evolve for gliomas, the direct costs related to treating brain tumors become more outdated. Estimates of the economics of brain tumors in the current era are needed. These studies should include detailed assessments of direct and indirect costs, including empirical data on out-of-pocket expenses. There is a need for an updated comprehensive study of the costs borne by patients with glioma, using a design that is specifically geared toward estimating these costs. Several authors have explored the variation in the methodologies used in cost of illness studies and the benefits and limitations of these methods.[43-45] A comprehensive longitudinal study, assessing the economic costs for patients with malignant gliomas, is needed.

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