View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

original research report

The challenges of managing glioblastoma multiforme in developing countries: a trade-off between cost and quality of care

Ahmed Salem, Sameh A. Hashem, Abdulla Al-Rashdan, Najeeb Ezam, Ala'a Nour, Amer Alsharbaji, Maher Sughayer, Issa Mohamad, Maher Elyan, Ala'a Addas, Maysa Al-Hussaini, Abdelatif Almousa

From the Department of Radiation Oncology, King Hussein Cancer Center, HM Queen Rania Hospital, Amman, Jordan

Correspondence: Abdelatif Almousa, MD · Department of Radiation Oncology, King Hussein Cancer Center, HM Queen Rania Hospital, Amman 11814, Jordan · T: +96265300460 · almousa@khcc.jo · Accepted August 2011

Hematol Oncol Stem Cell Ther 2011; 4(3): 116-120

DOI: 10.5144/1658-3876.2011.116

BACKGROUND AND OBJECTIVES: The management of glioblastoma multiforme (GBM) in developing countries is hindered by the paucity of clear protocols due in part to growing economic constraints and the lack of availability of expensive chemotherapeutic agents. We evaluated the deliverable treatment protocols and achievable outcomes for patients with GBM in a low-income country prior and subsequent to the worldwide adoption of temozolomide.

DESIGN AND SETTING: Retrospective case series.

PATIENTS AND METHODS: Charts of consecutive patients with a pathologic diagnosis of high-grade glioma diagnosed between January 2003 and December 2008 were retrospectively reviewed.

RESULTS: We identified 146 adult patients, including 105 males and 41 females between 19 and 81 years of age (median age, 51 years), with histologically confirmed high-grade glioma. All patients underwent craniotomy. Eighty-two patients were treated with radiotherapy and temozolomide, of whom 42 patients received temozolomide concurrent with radiation followed by adjuvant temozolomide; 40 patients received irradiation followed sequentially by 6 cycles of temozolomide. In 40 patients irradiation was utilized as a single modality treatment adjuvant to surgery. The follow-up ranged from 1 to 56 months (median, 9.4 months). The median survival for the whole cohort was 10.2 months. The median survival for the radiotherapy-alone group was 5.3 months and for combined radiotherapy/temozolomide was 14.8 months. Survival was similar in both concurrent and sequential groups. Temozolomide conferred a statistically significant survival benefit of 9 months compared with standard therapeutic modalities.

CONCLUSIONS: The results compare favorably to those reported in developed nations. Current management of GBM in developing countries should include maximal surgical resection followed by radiotherapy/temozolomide whenever medically and/or financially feasible. Outcomes comparable to those obtained within the context of randomized trials can be expected in low-income settings if healthcare delivery is carefully planned. Our results indicate that concurrent and sequential regimens are equally effective in these patients.

Despite the widespread adoption of multimodality therapy, the diagnosis of glioblastoma multiforme (GBM) continues to carry a dismal prognosis with a grave overall survival estimate set at 9 to 12 months.[1-3] Surgery followed by radiotherapy was considered the standard of care.[3] Temozolomide (TMZ) administered in addition to adjuvant radiotherapy (RT) has been shown to significantly prolong overall survival.[4] Currently, TMZ concurrent with RT followed by adjuvant TMZ (RT/TMZ regimen) has been adopted as the new standard of care in most developed countries. In contrast, the management of patients with GBM in developing countries is still hindered by the paucity of clear protocols due in part to growing economic restraints and the lack of availability of expensive chemotherapeutic agents. As a consequence, growing debate is unfolding as to whether the addition of an expensive chemotherapeutic agent is justifiable in

limited-resource countries. Does the addition of TMZ translate into overt survival benefit in these patients? In this retrospective review we report the typical management of patients with GBM in a low-income country highlighting the heterogeneity of treatment delivery and the achievable outcomes.

PATIENTS AND METHODS

Charts of consecutive patients with a pathologic diagnosis of high-grade glioma diagnosed and treated at King Hussein Cancer Center (KHCC) between January 2003 and December 2008 were retrospectively reviewed following acquisition of institutional review board approval in an attempt to extract data pertaining to pathological characteristics, clinical status, therapeutic alternatives and disease outcome. Records of imaging studies were made available for this review. Patients ≤18 years of age at the time of diagnosis were excluded from this case series. Pre-treatment performance status was evaluated according to the Karnofsky performance indicator (KPS) scale with 70% defined as the cut-off score.[5] Surgical resection status was designated as partial if only biopsy or partial resection was performed or aggressive if an attempt at resection was undertaken including near total, subtotal and gross total resection. Kaplan-Meier survival analysis was utilized to assess overall survival independent and dependent of various treatment modalities and variables. A *P* value ≤.05 was considered statistically significant. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

One hundred forty five patients met the eligibility criteria (**Table 1**). The group included 105 males and 41 females between 19 to 81 years in age (median age, 51 years). Seventy-five patients had KPS ≥70%. One hundred and thirty patients (89%) harbored supratentorial tumors. Assessment of tumor size was possible in all but six patients and ranged from 2 to 10.5 cm. The median tumor size of 5.5 cm was elected as a cut-off tumor size for evaluation of potential prognostic variables. In 44 patients (30%) the tumor size was <5.5 cm, while in 95 patients (65.5%) the tumor was ≥5.5 cm. All patients underwent craniotomy. The extent of surgical resection depended on the location and size of the tumor, patient performance and disease extent. Sixty-seven patients (46%) underwent biopsy, while surgical resection was performed in 78 patients (54 %). Upon pathological examination and immunohistochemical confirmation by glial fibrillary acidic protein, GBM was found in 141 patients. Specimens from the 4 patients who harbored gliosarcoma revealed evidence of mesenchymal differentiation and increased deposition of reticulin in areas of sarcomatomous differentiation.

Table 1. Characteristics of all patients (n=145).

		Number of patients	Percent
Gender	Male	104	72
	Female	41	28
Location	Supratentorial	129	89
	Infratentorial	11	7.5
	Multifocal	5	3.5
Size	Range (cm)	1.6-10.5	
	Median (cm)		
	<5.5 cm	44	30
	≥ 5.5 cm	95	65.5
	Not assessed	6	4.5
Type of surgery	Biopsy	67	46
	Gross total resection	10	6.5
	Near total resection	5	3.5
	Partial resection	27	19
	Subtotal resection	36	25
Pathology	GBM	141	97
	Gliosarcoma	4	3
Adjuvant therapy	Concomitant RT/TMZ	42	29
	Sequential RT/TMZ	40	27.5
	TMZ alone	6	4
	RT alone	40	27.5
	No adjuvant therapy	17	12

RT: radiotherapy, TMZ: temozolomide

Following adoption of the Stupp et al. protocol in 2005,[4] our standard approach dictated RT concurrent with daily TMZ at a dose of 75 mg/m^2 to be followed by daily adjuvant TMZ at a dose of 150 mg/m^2 during days 1-5 of a 28-day cycle for six cycles initiated three to four weeks following completion of concurrent therapy. Eighty-eight patients (60.5%) received adjuvant TMZ, of which 82 received it in addition to RT (**Table 2**). In six patients TMZ was the sole adjuvant modality consequent to poor overall performance. Patients with unfavorable prognostic vari-

Table 2. The use of adjuvant RT in a cohort of patients.

Treatment groups	Number	Subgroups	Number
RT alone	40	Diagnosed before 2005	8
		Medically unfit for systemic treatment with TMZ	17
		Died before TMZ initiation	15
RT dose			
≥54 Gy	100	RT alone	24
		Sequential RT/TMZ	38
		Concomitant RT/TMZ	35
<54 Gy	22	Dose adjusted to 44-50 Gy according to the limiting tolerance of neighboring normal tissue	13
		Patients did not complete RT because of death	5
		RT was stopped due to deterioration in the general condition	4

Table 3. Characteristics of patients who received concomitant and sequential TMZ treatment as compared with patients who received radiotherapy alone.

	Concomitant RT/TMZ group (42 patients) n (%)	Sequential RT/ TMZ group (40 patients) n (%)	RT alone group (40 patients) n (%)
KPS ≥70%	26 (62)	26 (65)	12 (30)
Age ≤50	22 (52)	19 (47)	7 (18)
Aggressive resection	24 (57)	19 (48)	8 (20)
RT dose ≥54 Gy	35 (83)	38 (95)	24 (60)
Supra-tentorial location	38 (90)	35 (87)	24 (60)

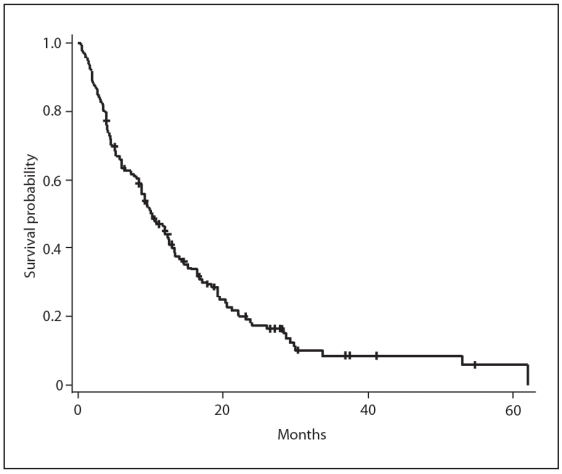

Figure 1. Kaplan-Meier estimate of overall survival for all patients with GBM.

ables were offered sequential RT/TMZ regimen in the form of RT followed by adjuvant TMZ after 3-4 weeks of rest in the form of 150 mg/m^2 during days 1-5 of a 28-day cycle for six cycles. In the remaining 42 patients, concurrent RT/TMZ regimen was offered (**Table 3**). Forty patients (27.5%) received RT alone as they were diagnosed prior to adoption of TMZ (2003-2004), consequent to poor overall condition and/or as a result of death prior to initiation of TMZ. The radiation dose ranged from 5400 to 6000 cGy and was delivered via conventional 1.8-2 Gy fractionation, 5 days per week for 5-6 weeks. In 13 patients, suboptimal radiation doses ranging from 4400 to 5000 cGy were delivered due to the dose-limiting tolerance limits of neighboring normal tissues. Five patients died during the course of radiation and in 4 patients RT was withheld due to deterioration of overall general condition. As such, 100 patients received RT at a dose of ≥5400 cGy and 22 patients received doses <5400 cGy. Seventeen patients received neither TMZ nor RT due to poor overall condition or medical contraindication for treatment. The majority died within 2 months.

At a median follow-up of 9.4 months (range, 1-56 months), the median survival for the whole cohort was 10.2 months (**Figures 1, 2**). The median survival for the RT-alone group was 5.3 months and for combined TMZ/RT was 14.8 months, with a median survival benefit of 9.4 months (P=.0009). The poor overall survival exhibited in the RT-alone group might be partially explained by the poor patient characteristics (**Table 3**). Survival was significantly better among patients with KPS ≥70%, age ≤50 years, RT dose ≥5400 cGy, among those who had more aggressive tumor resection and a supratentorial tumor location (**Figure 3**). Tumor size and gender did not confer any statistically significant difference in survival.

Using a stepwise Cox Hazard model, treatment (TMZ or TMZ/RT versus RT alone and aggressive surgical resection versus partial resection) and KPS status were the most significant factors impacting survival. The hazard ratio (HR) for RT as compared to TMZ/RT was 1.9 (95% confidence interval [CI], 1.25 to 3.01; P=.003) and for partial as compared to aggressive surgical resection was 1.96 (95% CI, 1.32 to 2.91; P=.0008). Additionally the HR for KPS <70% as compared to KPS ≥70% was 2.4 (95% CI, 1.6 to 3.6; P<.001). Surprisingly, and even though comparable in terms of patient demographics and tumor characteristics, concurrent and sequential RT/TMZ groups demonstrated similar overall survival and the unadjusted survival for RT/TMZ sequencing was not statistically

significant (*P*=.2535)

DISCUSSION

In Jordan, CNS malignancies account for 3.3% of all newly diagnosed malignant tumors, ranking the 8th most common cancer. Approximately 60% of all brain cancers are of astrocytic histology, of which GBM is the most common subtype.[6] Demographically, and in contrast to the US SEER data, approximately two-thirds of cases in Jordanians occur among patients younger than 50 years of age, a finding possibly explained by the differences in age demographics of both populations.[7] Nonetheless, patient demographic characteristics in this case review are comparable to those in previously published US reports.

The landmark phase III clinical trial conducted by European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) in 2004 clearly demonstrated that concurrent RT plus TMZ followed by six cycles of TMZ significantly prolonged survival, with a median survival benefit of 2.5 months compared to RT alone in patients with newly diagnosed GBM.[4] In the updated report published in 2009, survival benefit continued to be statistically significant at 5 years follow-up for the same cohort of patients.[8]

In Jordan, healthcare is delivered via national, university and private hospitals. National hospitals are funded, managed and operated by the Ministry of Health and provide near-global low-cost primary care coverage. University hospitals, on the other hand, deliver specialized tertiary care. Private hospitals deliver fee-for-service care. KHCC is the sole comprehensive cancer center in the country, treating approximately 70% of all cancer cases per year. Care is delivered via a multidisciplinary approach and is heavily evidence-driven. Unfortunately, several gaps hinder the provision of comprehensive quality care for GBM patients outside our institution including inappropriate clinical practices, insufficient implementation of evidence-based medicine and unbalanced physical distribution of care providers.[9] Similar therapeutic variations are normally observed among developing countries. The impact of scarce-resource allocation is of particular importance in low-income nations. This applies to expensive chemotherapeutic agents such as TMZ and intensity modulated radiation therapy. According to the EORTC 26981/22981 NCI-C CE3 Intergroup Study, the cost of TMZ for the mean survival benefit per life year is €37 361.[10]

The median survival of our cohort of patients is consistent with the established range in the literature.[1,4,11] Our review demonstrated that the addition of TMZ to RT is superior to RT alone, with a median improvement in survival of 9.4 months. Findings in this study compare favorably to those obtained via the EORTC/NCI trial with similar survival rates at 6, 12, 18 and 24 months (**Table 4, Figure 4**).

In conclusion, the addition of TMZ confers a significant survival benefit to patients with GBM. Current management of GBM in developing countries should include maximal surgical resection followed by RT/

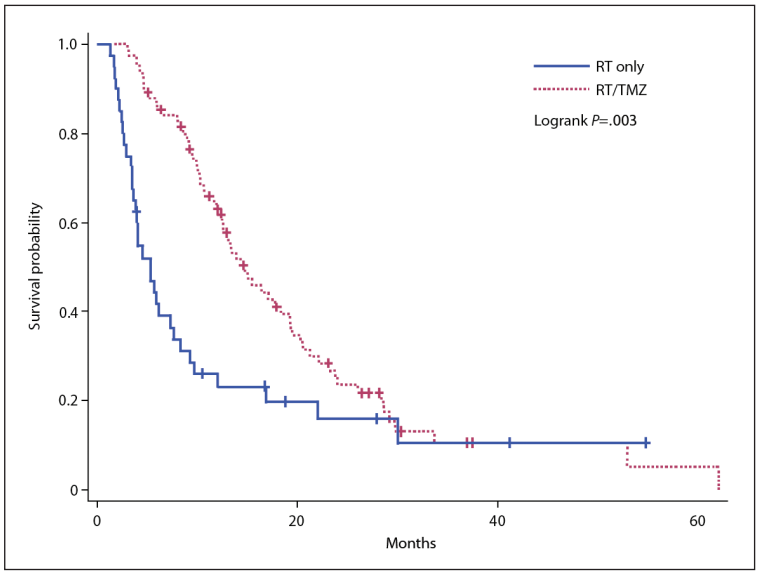

Figure 2. Kaplan-Meier estimate of overall survival for patients according to treatment modality.

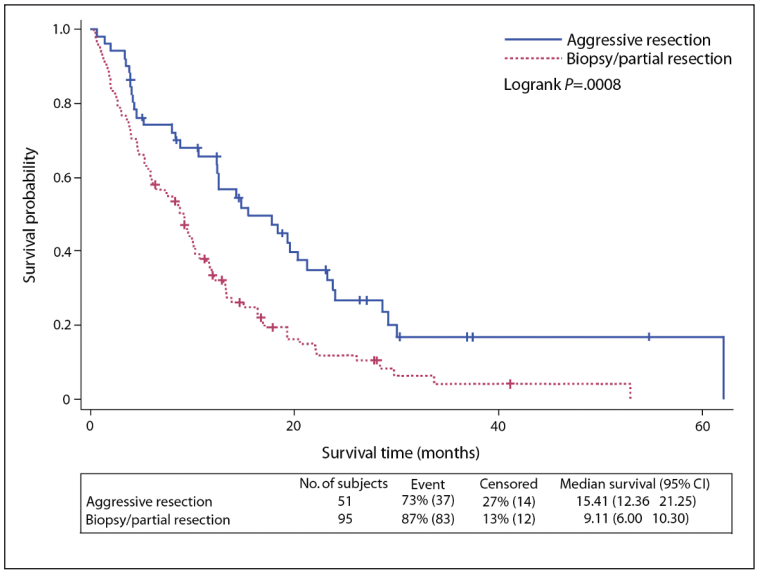

Figure 3. Overall survival of the entire cohort according to the extent of surgical resection.

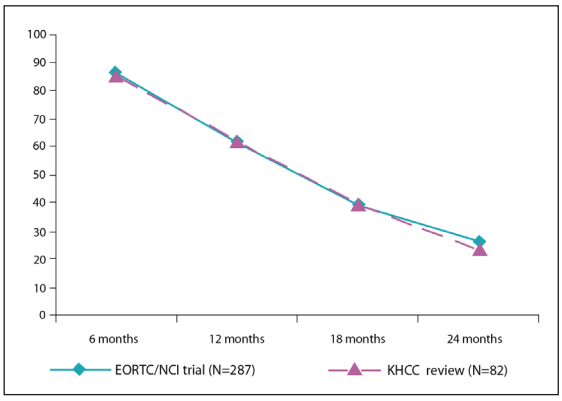

Figure 4. Survival for both studies for the RT-TMZ group.

Table 4. Comparison of survival for both studies.

RT/TMZ	EORTC/NCI trial (N=287)	KHCC review (N= 82)
Median survival (months)	14.6 (13.2-16.8)	14.75 (12.46-19.28)
At 6 months	86.3	85.3
At 12 months	61.1	61.8
At 18 months	39.4	39.6
At 24 months	26.5	23.5

TMZ whenever medically and/or financially feasible. Outcomes comparable to those obtained within the context of randomized trials can be expected in low-income settings if healthcare delivery is carefully planned. Our results indicate that concurrent and sequential RT/TMZ regimens are equally effective in these patients. We believe that a prospective randomized trial is warranted to confirm these unexpected findings.

We would like to thank Ms. Ayat Taqash for her efforts in the completion of the statistical analysis of this paper.

Author contributions

All authors had an equal contribution to drafting and review.

The authors declare no conflict of interest.

Acknowledgment

REFERENCES

1. Kristiansen K, Hagen S, Kollevold T, Torvik A, Holme I, Nesbakken R, Hatlevoll R, Lindgren M, Brun A, Lindgren S, Notter G, Andersen AP, Elgen K. Combined modality therapy of operated astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. Cancer 1981;47:649-652.

2. Chamberlain MC, Kormanik PA. Practical guidelines for the treatment of malignant gliomas. West J Med 1998;168:114-120.

3. Walker MD, Alexander E Jr, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J Jr, Norrell HA, Owens G, Ransohoff J, Wilson CB, Gehan EA, Strike TA. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg. 1978 Sep;49(3):333-43.

4. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-996.

5. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2:187-193.

6. Tarawneh M, Nimri O. Jordan National Cancer Registry 2007. Vol 12. 12 ed. Amman: Ministry of Health 2007.

7. Peter D I, Elain Ron MECC Monograph : Brain and Other Central Nervous System Cancer; 2001.

8. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-466.

9. Al-Jauissy MS, Al-Hassan M, Akhu-Zaheya L. Healthcare needs of noninstitutionalized Jordanian cancer patients: an exploratory descriptive study. Cancer Nurs. 2009 Jul-Aug;32(4):291-8.

10. Lamers LM, Stupp R, van den Bent MJ, Al MJ, Gorlia T, Wasserfallen JB, Mittmann N, Jin Seung S, Crott R, Uyl-de Groot CA; EORTC 2698½2981 NCI-C CE3 Intergroup Study. Cost-effectiveness of temozolomide for the treatment of newly diagnosed glioblastoma multiforme: a report from the EORTC 2698-2981 NCI-C CE3 Intergroup Study. Cancer 2008;112:1337-1344.

11. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001;95:190-198.