ORIGINAL ARTICLE ◄

Glioblastoma Multiforme, Long-term Survival (Single Institution Experience)

Mohamed A Hassan[1], Noha Y Abdou[2], Dalia O Darwish[3]

(1) Professor of Clinical Oncology, NEMROCK, Faculty of medicine, Cairo University, Egypt.
(2) Lecturer of Clinical Oncology, NEMROCK, Faculty of medicine, Cairo University, Egypt.
(3) Lecturer of Clinical Oncology, NEMROCK, Faculty of medicine, Cairo University, Egypt.

✉ *Corresponding Author: Dalia Omar Darwish, Department of Radiation Oncology (NEMROCK), Faculty of medicine, Cairo University, Egypt, E-mail: daliaomard@yahoo.com*

Key words: Glioblastoma mutiforme, Long term survival.

Submitted: 16 January 2009; Accepted: 31 January 2009

ISSN: 2070-254X

Abstract

Purpose: Patients with glioblastoma multiforme (GBM) have very poor prognosis; the median survival with the best available treatment is only 12 months. The survival rate has changed little in the past 20 years. This clinico-epidemiological study was prompted to identify specific parameters that might be associated with GBM patients who have achieved an unusual overall survival of >36months post diagnosis.

Patients and Methods: In this clinicoepidemiological study, the frequency of long-term glioblastoma multiforme (GBM) survivors (LTGBMSs) was determined in a population-based study. All patients diagnosed with GBM and referred to Kasr El Aini Center of Radiation Oncology from January 1995 till December 2002 were included in the study. Patients were followed up, and LTGBMSs were defined as GBM patients surviving 3 years or more after diagnosis. Patients were compared in terms of age, sex, and year of diagnosis with standard survivors. Analysis of clinicoepidemiological factors related to survival issues was attempted trying to identify prognostic factors associated with prolonged survival.

Results: One hundred and forty three GBMs patients were diagnosed in the study period; 7 (4.66%) of these patients survived 3 years or more. LTGBMSs (mean age, 38.1 years) were significantly younger when compared with all GBM patients (mean age, 52 years). LTGBMSs had a higher Karnofsky Performance Status score at diagnosis. LTGBMSs were much more likely to have had a gross total resection and adjuvant chemotherapy than the standard GBM patients.

Conclusion: Conventionally treated GBM patients in an unselected population have a very small chance of long-term survival. Aggressive surgical resection as well as adjuvant chemotherapy in addition to sophisticated radiation therapy techniques might contribute to better survival outcome in such dismal disease, particularly in selected patients with young age, good performance status and following near or total resection.

Introduction

Glioblastoma multiforme is the most malignant primary tumour of the brain and it is associated with one of the worst 5-year survival rates among all human cancers. The prognosis for patients with glioblastoma multiforme (GBM) is very poor; the median survival with the best available treatment is only 12 months. The survival rate has changed little in the past 20 years despite the multimodal aggressive treatment.1,2

The role of the current study is to determine whether a clinico-epidemilogical reexamination of putative long-term GBM survivors (LTGBMSs) would uncover certain prognostic factors that are associated with favorable prognosis.3–6 LTGBMSs have been described by others7–15 as uncommon, occurring in 1% to 17% of GBM patients. The factors reported in these studies associated with long-term survival included the use of multimodality therapy, young age, and high performance status at the time of diagnosis.7,8,11–14 However, there are limitations of these reports. Previous comparisons between LTGBMSs and their shorter surviving counterparts have been uncontrolled for known prognostic factors such as age and Karnofsky performance status. The powerful prognostic effect of these might mask other unidentified prognostic characteristics specific for long-term survival.

This study was designed to determine the frequency of LTGBMSs in patients presented and treated in NEMROCK between the year 1995 and 2002 and to identify prognostic factors associated with patients who have long-term survival.

Patients and Methods

Patient Selection Criteria

All patients diagnosed with GBM and referred to Kasr El Aini Center of Radiation Oncology from January 1995 till December 2002 were included in the study. Patients were followed up, and LTGBMSs were defined as GBM patients surviving 3 years or more after diagnosis and their clinicoepidemiological data was analyzed in relation to survival parameters.

These factors included age, sex, and treatment that predicted long-term survival. Functional status at diagnosis was determined by using the Karnofsky Performance Status (KPS) scale. Age was defined at the time of initial imaging. Extent of surgical resection was defined as biopsy (10% resected), subtotal resection (10–90% resected), or gross total resection (90% resected).12

Statistical Analysis

Statistical analyses were performed according to the Statistical Analysis System (SAS Institute, SAS/STAT User's Guide, Version 6, fourth edition, Cary, NC). The data were expressed as mean standard error of the mean (SEM). Univariate

and multivariate conditional logistic regression were used to examine the influence of prognostic variables.16

Results

We identified 143 GBM patients who were diagnosed and treated in Kasr El Aini hospital over 7 years. Seven of them were long-term survivors. There were 2 females and 5 males LTGBMSs Table (1). The LTGBMSs were significantly younger (mean age, 38.1 years) when compared with other GBM patients diagnosed in the study period (mean age, 52 years) (p, 0.02). The LTGBMSs had a significantly longer mean survival time of 50.85months (range, 38–84 months) compared with only 14.4 months (range, 2–35 months) for the control GBM patients (p , 0.001). Treatment given for the long-term survivors is summarized in Table (2).

Clinical Comparisons between LTGBMSs and Control GBM Patients

A comparison of the clinical features of LTGBMSs and standard survival GBM patients is summarized in Table (3). LTGBMSs had a significantly higher level of function (mean KPS, 84.2) than the controls (mean, 76.1) (p ,0.02) at the time of diagnosis. The period of symptom duration before diagnosis was significantly longer in the LTGBMSs (mean, 21.7 weeks) than controls (mean, 10.6 weeks) (p, 0.05). LTGBMSs had a much higher incidence of seizures as their presenting symptoms compared with controls, although this did not reach statistical significance. Other clinical factors were similar between the two groups. One of 7 (14%) LTGBMSs, for which sufficient follow-up information was available was demented.

Treatment Comparisons between LTGBMSs and Control GBM Patients

As shown in Table (3), LTGBMSs were much more likely to have had a gross total resection (4 of 7, or 57.2%) than control GBM patients (20 of 136, or 14%) (p > 0.001). Postoperatively, all patients received external beam radiation therapy except 2 control patients who died either before it could be started or completed. For patients who completed radiation therapy there was no significant difference in the total radiotherapy dose used between LTGBMSs (5600 cGy) and control (5400 cGy) patients. There were more LTGBMSs (4 of 7, or 57.2%) who had adjuvant chemotherapy than controls (0 of 136, or 0%), however not reaching statistical significance (p, 0.3). The chemotherapies included CCNU [N-(2-chloroethyl)-N9-cyclohexyl-N-nitrosourea, or lomustine], cisplatin-vepsid, and temozolamide given as part of initial tumor management or at tumor recurrence.

Discussion

This study shows that long-term survival is possible in GBM patients but is an uncommon entity. Only 4.6% of patients in our population-based study survived more than 3 years. Conventionally treated patients with GBMs have both a short median survival1,2 and a very small chance of long-term survival. Despite controlling for age, patients who were aggressively treated with maximal surgical resection and adjuvant chemotherapy were more likely to be long-term survivors.

Our results support previous reports8,12,13 that showed that aggressive treatment makes long-term survival more likely. Adjuvant chemotherapy did not show prolongation in median survival in GBM patients although it is commonly used. However the present study and others17,18 might suggest that adjuvant chemotherapy will make long-term survival more likely.

The usefulness of maximal surgical resection in GBM patients is unknown, because a prospective trial has never been done, but there are strong proponents on both sides of this controversy.19–25 Our results support the role of surgery to improve long-term survival in certain GBM patients.

The combination of aggressive surgical resection followed by adjuvant radiotherapy and chemotherapy may further improve a patient's likelihood of long-term survival if the performance status at the time of diagnosis is high (i.e. KPS 70). However, we are limited to describing associations, and causal statements cannot be made, as a significant selection bias exists. It is likely that the treating physicians offered more aggressive therapy to patients whom they believed had the greatest chance of long-term survival.26,27

Dementia and loss of independence may be the usual outcomes for certain LTGBMSs and malignant glioma survivors when aggressive therapy successfully controls the tumor, however that was not recognized in our study.9,28

Our study has several limitations. First, it is a retrospective analysis and limited to existing documentation and available patient data, which was incomplete in several cases. Furthermore, we relied on operative reports in some cases to assess the extent of surgical resection. Another limitation is the small number of LTGBMS patients in comparison to the control group. Finally, it was not possible to perform multivariate analysis to determine which of the factors we identified was the most important. Thus, LTGBMS may only be a statistical effect where these patients are the extreme of a distribution but are not categorically different.

Conclusion

This population-based study of GBM patients shows that long-term survival is rare and highlights the clinical challenge of this disease. Aggressive surgical resection and adjuvant chemotherapy favor long-term survival in patients with a high (KPS, 70) performance status.

References

1. Barnholtz-Sloan JS, Sloan AE, Schwartz AG. Relative survival rates and patterns of diagnosis analyzed by time period for individuals with primary malignant brain tumor, 1973–1997. J Neurosurg. 2003; 99:458–66.

2. Forsyth PA, Cairncross JG. Treatment of malignant glioma in adults. Curr Opin Neurol. 1995; 8:414–418.

3. Homma T, Fukushima T, Vaccarella S, et al. Correlation among pathology, genotype, and patient outcomes in glioblastoma. J Neuropathol Exp Neurol. 2006; 65:846–54.

4. Daumas-Duport C, Scheithauer B, O'Fallon J, et al. Grading of astrocytomas: a simple and reproducible method. Cancer. 1988; 62:2152–2165.

5. Shinojima N, Kochi M, Hamada J, et al. The influence of sex and the presence of giant cells on postoperative long-term survival in adult patients with supratentorial glioblastoma multiforme. J Neurosurg. 2004; 101:219–26.

6. Balmaceda C, Goldman J, Fetell MR. Long-term survival in malignant astrocytomas re-evaluated: are they really oligodendrogliomas. Neurology. 1996; 46:A451.

7. Dietmar Krex, Barbara Klink, Christian Hartmann, et al. Long-term survival with glioblastoma multiforme. Brain. 2007; 130 (10):2596-2606.

8. H. Yoon, A. F. Hottinger, L. M. DeAngelis, et al. Clinical outcome of glioblastoma multiforme patients with long-term survival. Journal of Clinical Oncology, 2007; Vol 25, No. 18S : 2069.

9. Prabal Deb, Mehar Chand Sharma, Ashok Kumar Mahapatra, et al. Glioblastoma multiforme with long term survival. Neurol India. 2005; 53:329-32.

10. Steinbach JP, Blaicher HP, Herrlinger U, et al. Surviving glioblastoma for more than 5 years: the patient>s perspective. Neurology. 2006; 66:239–42.

11. McLendon RE, Halperin EC. Is the long-term survival of patients with intracranial glioblastoma multiforme overstated? Cancer. 2003; 98:1745–8.

12. Scott JN, Rewcastle NB, Brasher PM, et al. Which glioblastoma multiforme patient will become a long-term survivor? A population-based study. Ann Neurol. 1999; 46:183–8.

13.Salcman M, Scholtz H, Kaplan RS, et al. Long-term survival in patients with malignant astrocytoma. Neurosurgery 1994; 34: 213–220.

14. Morita M, Rosenblum MK, Bilsky MH, et al. Long-term survivors of glioblastoma multiforme: clinical and molecular characteristics.J Neurooncol 1996; 27:259–266.

15. Olivera C, Bartley M, Ferrall S, et al. Long-term malignant glioma survivors over ten years: prognostic factors. ProcASCO 1997;16:407a.

16. SAS Institute Inc. (1990), SAS/STAT User's Guide, Version 6, Fourth Edition, Vol. 1 & 2, Cary, NC: SAS Institute Inc.

17. Fine HA. The basis for current treatment recommendations for malignant gliomas. J Neurooncol 1994; 20:111–120.

18. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med, 2005; 352:987–96.

19. Nazzaro JM, Neuwelt EA. The role of surgery in the management of supratentorial intermediate and high-grade astrocytomas in adults. J Neurosurg 1990;73:331–344.

20. Devaux BC, O'Fallon JR, Kelly PJ. Resection, biopsy, and survival in malignant glial neoplasms. J Neurosurg 1993; 78:767–775.

21. Kreth FW, Warnke PC, Scheremet R, et al. Surgical resection and radiation therapy versus biopsy and radiation therapy in the treatment of glioblastoma multiforme. J Neurosurg 1993;78:762–766.

22. Berger MS. Malignant astrocytomas: surgical aspects. Semin Oncol 1994; 21:172–185.

23. Rostomily RC, Keles GE, Berger MS. Radical surgery in the management of low-grade and high-grade gliomas. Clinical neurology. 1996:345–369.

24. Kowalczuk A, Macdonald RL, Amidei C, et al. Quantitative imaging study of extent or surgical resection and prognosis of malignant astrocytomas. Neurosurgery. 1997; 41:1028–1038.

25. Wisoff JH, Boyett JM, Berger MS, et al. Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group Trial No. CCG-945. J Neurosurg. 1998; 89:52–59.

26. Salford L, Brun A, Nirfalk S. Ten-year survival among patients with supratentorial astrocytomas grade III and IV. J Neurosurg 1988; 69:506–509.

27. Cairncross JG, Macdonald DR, Ludwin S, et al. Chemotherapy for anaplastic ologodendroglioma: National Institute of Canada Clinical Trials Group. J Clin Oncol 1994; 12: 2013–2021.

28. Archibald YM, Lunn D, Ruttan LA, et al. Cognitive functioning in long-term survivors of high grade glioma. J Neurosurg 1994; 80:247–253.

Tables

Table 1. Clinico-epidemiological characteristics of LTGBM

N	Age yr/sex	KPS	Presenting symptoms	Symptom duration wks	Status	Survival m
	30/M	80	Hp	8	MPR	84m
	21/M	90	H	12	CR	48m
	31/M	60	Hp	91	MPR	57m
	39/M	80	Hp	10	MPR	38m
	46/F	90	Sz	11	CR	40m
	49/F	90	Sz	8	CR	39m
	51/M	100	V	12	CR	50m

LTGBM: long term glioblastoma multiform KPS: Karnofsky performance status HP:Hemipareisis Sz: Seizure V: vision CR: complete remission MPR: Major partial remission.

Table 2. Treatment of the 7 long term survivors with intracranial Glioblastoma multiforme

N	Sex	Age	Surgery			Radiotherapy	Chemotherapy Line of treatment		
			CR	IR	EB	Dose Gy	CCNU	Temozolamide	Cisplatin -VP16
1	M	30	+			5600	1st	2nd	
2	M	21		+		5600	1st	2nd	
3	M	31			+	5600	1st		2nd
4	M	39			+	5600		1st	2nd
5	M	46	+			5600			
6	M	49	+			5600			
7	M	51	+			5400			

CR: complete resection, IR: incomplete resection, EB: excision biopsy

Table 3. Clinical comparison between LTGBMS and control GBM patients

Factor	LTGBMS N :7	Control N :136	P value
KPS			
Mean	84.2	76	
Range	60-100	40-90	
Symptom duration wks			
Mean	21.7w	11w	
Range	8-91	1-156	
Presenting symptom			
Seizure	2 28.6%	31 23%	0.5
Hemiparesis	3 42.8%	44 32%	0.5
Headache	1 14.3%	72 53%	0.02*
Visual symptoms	1 14.3%	16 12%	0.2
Personality changes	0	35 26%	0.2
Surgical excision			
Gross total resection	4 57.2%	20 14%	>0.001**
Subtotal resection or biopsy	3 42.8%	123 86%	
Radiation therapy cGy			
Mean	5600	5400	
Chemotherapy	4 57.2%	0 0%	0.3

* P<0.05= significant, **P<0.01= highly significant