Original Article

Haematological outcome of concomitant chemoradiation with Temozolomide (CCRT) versus radiation therapy (RT) alone in patients with high grade gliomas

Rasheed MMO[1], Bhuiyan MZR[2], Sharmin S[3], Rahman A[4], Hossain MM[5], Kader KM[6]

Abstract

High grade gliomas(HGG) are the most common primary CNS tumors in adult. Even with multidisciplinary approach, the outcome is miserable. However recently concomitant chemoradiation (CCRT) with temozolomide has been effectively used with increase in median survival & good clinical outcome. This quasi experimental study was done in the department of Radiation Oncology in National Institute of Cancer Research & Hospital (NICRH) Mohakhali , Dhaka during January 2014 to December 2014. Sixty patients with newly diagnosed & histologically proved high grade glioma were assigned to receive either radiation therapy alone (fractionated focal irradiation in daily fractions of 2 Gy in five fractions per week for six weeks, for a total 60 Gy) or radiation therapy plus Temozolomide(75 mg/m^2 from 1st day of radiation therapy to last day of radiation therapy) followed by six cycles of adjuvant temozolomide (150 to 200mg per square meter for five days during each 28 day cycle). Haematological abnormalities and neurotoxicities were compared between the patients of two arms. Patients treated CCRT showed more toxicities than the radiation therapy alone in some stages. As a whole the differences were not statistically significant.

Key words: High grade gliomas, concomitant chemo-radiation with temozolomide, radiation therapy

1. *Dr Md Mamun Or Rasheed, Medical Officer, Department of Oncology, BSMMU, Dhaka
2. Dr Md Zillur Rahman Bhuiyan, Associate Professor, Department of Oncology, BSMMU, Dhaka
3. Dr Sadia Sharmin, Assistant Professor, Department of Oncology, BSMMU, Dhaka
4. Dr Atiar Rahman, Assistant Professor, Department of Transfusion Medicine, BSMMU, Dhaka
5. Dr Md Monoar Hossain, Assistant Professor, Department of Surgical Oncology, BSMMU, Dhaka
6. Professor Dr Kazi Manzur Kader, Department of Radiation Oncology, NICRH, Dhaka

**For correspondence*

Introduction

Primary brain tumors comprise only approximately 2 % of all the malignant diseases.[1] However, the major data source - surveillance, epidemiology and end results(SEER) reported an incidence of 6.5 per 100000 persons. More than 17000 cases are diagnosed every year in the united states and among them approximately 13,000 die every year.[2]

More specific CNS tumor types also differ in incidence rate based on anatomical location and also with age.[3] Gliomas constitute 40 percent of all primary CNS tumors.[4] Two third of gliomas are high grade, which comprises the glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), anaplastic oligodendroglioma, anaplastic oligoastrocytoma and less commom varieties such as anaplastic ependymoma and anaplastic ganglioglioma.[5] Male to female ratio among affected patient is about 3:2 and most of the HGG are sporadic, although they are associated with genetic syndromes.[6,7] The peak age of onset for anaplastic astrocytoma is during the 4th and 5th decade, while GBM generally presented in the 6th and 7th decade.[8]

There are several presumed reasons for miserable outcome of high grade gliomas. First the tumor cells in GBM extensively infiltrate the surrounding brain parenchyma, thereby limiting the overall utility of surgical resection. Second the blood brain barrier is an obstacle to the adequate delivery of chemotherapy agents to brain tumors.[9] Third HGG is resistant to most cytotoxic agents, the expression of MGMT promoter methylation is thought to be the major mechanism of the resistance.[10] Therefore surgical resections alone is the limitation in the treatment of HGG.[11] HGG have high morbidity and mortality rate, even with optimal, treatment median survival is only 12 to 15 months and 2 years survival rate in the range of only 8 to 12 percent for glioblastoma multiforme and 2 to 7 years for anaplastic astrocytoma.[12] Without any treatment the median survival is only 3 to 6 months from the time of diagnosis.[13] The standard management of HGG involve cytoreduction by surgical resection when feasible followed by radiation therapy with or without adjuvant chemotherapy.[13] Adjuvant radiation therapy helps to decrease local failure, delays recurrence and prolong survival up to 12 months.[14]

Most recently, the effectiveness of this concomitant chemotherapy with Temozolomide has also been reported in many studies. The results of many trials demonstrated that concomitant radiation therapy plus continuous daily Temozolomide therapy followed by additional cycles of the standard regimen of adjuvant Temozolomide therapy is well tolerated and may prolong survival in patient with malignant glioma.[12] Temozolomide is very easy to administer and safe to handle and also produced by our domestic pharmaceuticals.

Methods

This quasi experimental study was done in the department of Radiation Oncology in National Institute of Cancer Research & Hospital (NICRH) Mohakhali , Dhaka during January 2014 to December 2014.

Sixty patients with newly diagnosed & histologically proved high grade glioma with a age range of 18-70 and of both sexes years were enrolled as study population. All patients had a UICC performance status at and below 70. They were divided in to two arms, Arm A and Arm B, and assigned to receive either radiation therapy alone (fractionated focal irradiation in daily fractions of 2 Gy in five fractions per week for six weeks, for a total 60 Gy - conventional) or radiation therapy plus Temozolomide (75 mg/m^2 from 1st day of radiation therapy to last day of radiation therapy - experimental) followed by six cycles of adjuvant temozolomide (150 to 200mg per square meter for five days during each 28 day cycle).

Prior to treatment, evaluation of hematological, renal and hepatic functions was done and absolute neutrophil count >15/mL, platelet count > 100000 / mL, hemoglobin >10 gm/dl, serum creatinine and total serum bilirubin less than 1.5 times the upper limit of normal and AST less than twice the upper limit of normal were ensured. Poor general physical conditions were not taken into account. Pre-treatment evaluation of tumor for planning and outcome prediction, computed tomography (CT), magnetic resonance imaging (MRI) was also done. Follow- up were done weekly & included included physical examination and full blood counts. Antiemetic prophylasix was also given before the initial doses of concomitant Temozolomide and was continued during the adjvant five days courses of temozolomide.

Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0, with a score of 1 indicating mild adverse effects, a score of 2

Table -I: Distribution of the patients by thrombocytopenia toxicity.

Thrombocytopenia Toxicity		Experimental (Arm A)		Conventional (Arm B)		p-value*
		n	%	n	%	
At the beginning	Grade 0	30	100.0	30	100.0	-
7 days after treatment	Grade 0	29	96.7	29	96.7	1.000
	Grade 1	1	3.3	1	3.3	
14 days after treatment	Grade 0	29	96.7	29	96.7	1.000
	Grade 1	1	3.3	0	0.0	
	Grade 2	0	0.0	1	3.3	
21 days after treatment	Grade 0	30	100.0	29	96.7	1.000
	Grade 2	0	0.0	1	3.3	
28 days after treatment	Grade 0	29	96.7	29	96.7	1.000
	Grade 1	1	3.3	0	0.0	
	Grade 2	0	0.0	1	3.3	
after 1st cycle of TMZ	Grade 0	30	100.0	30	100.0	-
After 2nd cycle of TMZ	Grade 0	30	100.0	30	100.0	-
after 3rd cycle of TMZ	Grade 0	30	100.0	30	100.0	-
after 4th cycle of TMZ	Grade 0	29	96.7	30	100.0	1.000
	Grade 1	1	3.3	0	0.0	
After 5th cycle of TMZ	Grade 0	30	100.0	30	100.0	
after 6th cycle of TMZ	Grade 0	29	96.7	30	100.0	1.000
	Grade 1	1	3.3	0	0.0	

* Fisher's Exact test

moderate adverse effects, a score of 3 severe adverse effects and a score of 4 life threatening adverse effects.

Results

Haematological toxicities were compared between the patients of two arms. Patients treated by CCRT with Temozolomide showed more toxicities than the conventional radiation treatment alone in some stages. As a whole the differences were not significant.

Thrombocytopenia toxicity was compared in 11 different periods of time. At the beginning of the treatment all patients in both arms showed grade 0 toxicities. At day 7 of the treatment in Arm A, 1 patient reported with grade 1 thrombocytopenia toxicity in both arms. All other patients showed grade 0 thrombocytopenia toxicity. At day 14 of treatment 1 patient of Arm B showed grade 2 thrombocytopenia toxicity; at 21 days of the treatment 1 patient in arm B had grade 2 thrombocytopenia toxicity. At 28 days after treatment in arm A, one patient showed grade 1 thrombocytopenia toxicity and in arm B one patient had grade 2 thrombocytopenia toxicity.

Thrombocytopenia toxicities after 1st cycle to 3rd cycle of TMZ treatment were identical in both arms i.e. all the patients showed grade 0 thrombocytopenia toxicities. After 4th and 6th cycles of TMZ treatment 1 patient in arm A showed grade 1 thrombocytopenia toxicity. Grade 0 thrombocytopenia toxicities were noted in 5th cycle of TMZ in both arms. However, no differences of thrombocytopenia toxicities were statistically significant between these two arms (p>0.05). (Table-I)

WBC toxicity is compared in 11 different periods of time. At day 7 of the treatment in Arm A, 1 patient reported with grade 1 WBC toxicity while all patients in Arm B showed

Table -II: Distribution of the patients by WBC toxicity.

WBC toxicity		Experimental (Arm A)		Conventional (Arm B)		p-value*
		n	%	N	%	
At the beginning	Grade 0	29	96.7	30	100.0	1.00
	Grade 1	1	3.3	0	0.0	
7 days after treatment	Grade 0	29	96.7	29	96.7	1.00
	Grade 1	1	3.3	1	3.3	
14 days after treatment	Grade 0	30	100.0	29	96.7	1.00
	Grade 1	0	0.0	1	3.3	
21 days after treatment	Grade 0	28	93.3	29	96.7	0.492
	Grade 1	2	6.7	0	0.0	
	Grade 2	0	0.0	1	3.3	
28 days after treatment	Grade 0	27	90.0	29	96.7	0.237
	Grade 1	3	10.0	0	0.0	
	Grade 2	0	0.0	1	3.3	
after 1st cycle of TMZ	Grade 0	30	100.0	30	100.0	-
After 2nd cycle of TMZ	Grade 0	30	100.0	30	100.0	-
after 3rd cycle of TMZ	Grade 0	30	100.0	30	100.0	-
after 4th cycle of TMZ	Grade 0	29	96.7	30	100.0	1.00
	Grade 1	1	3.3	0	0.0	
After 5th cycle of TMZ	Grade 0	29	96.7	30	100.0	1.00
	Grade 2	1	3.3	0	0.0	
after 6th cycle of TMZ	Grade 0	29	96.7	30	100.0	1.00
	Grade 2	1	3.3	0	0.0	

* Fisher's Exact Test

Table -III: Distribution of the patients by Hb% toxicity.

Haemoglobin toxicity		Experimental (Arm A)		Conventional (Arm B)		p-value*
		n	%	N	%	
At the beginning	Grade 0	30	100.0	30	100.0	-
7 days after treatment	Grade 0	29	96.7	29	96.7	1.00
	Grade 1	0	0.0	1	3.3	
	Grade 2	1	3.3	0	0.0	
14 days after treatment	Grade 0	30	100.0	29	96.7	1.00
	Grade 2	0	0.0	1	3.3	
21 days after treatment	Grade 0	30	100.0	29	96.7	1.00
	Grade 2	0	0.0	1	3.3	
28 days after treatment	Grade 0	25	83.3	29	96.7	0.195
	Grade 1	4	13.3	1	3.3	
	Grade 2	1	3.3	0	0.0	
after 1st cycle of TMZ	Grade 0	29	96.7	30	100.0	1.00
	Grade 1	1	3.3	0	0.0	
After 2nd cycle of TMZ	Grade 0	30	100.0	30	100.0	-
after 3rd cycle of TMZ	Grade 0	30	100.0	30	100.0	-
after 4th cycle of TMZ	Grade 0	28	93.3	30	100.0	0.492
	Grade 1	2	6.7	0	0.0	
After 5th cycle of TMZ	Grade 0	29	96.7	30	100.0	1.00
	Grade 1	1	3.3	0	0.0	
after 6th cycle of TMZ	Grade 0	29	96.7	30	100.0	1.00
	Grade 1	1	3.3	0	0.0	

* Fisher's Exact test

grade 0 WBC toxicity. At day 14 of treatment only 1 patient of Arm B showed grade 1 WBC toxicity; at 21 days of the treatment 2 patients in Arm A had grade 1 toxicity while one patient in Arm B had grade 2 WBC toxicity. At 28 days after treatment in Arm A, three patients showed grade 1 toxicity. However, in Arm B one patient had grade 2 WBC toxicity. WBC toxicities after 1st cycle to 3rd cycle of TMZ treatment were identical in both arms i.e. all the patients showed grade 0 WBC toxicities. After 4th cycle of TMZ treatment 1 patient in Arm A showed grade 1 toxicity. Identical WBC toxicities were noted in 5th and 6th cycle of TMZ where one patient in both arm showed grade 2 toxicities. However, no difference of WBC toxicity was statistically significant between these two arms (p>0.05). (Table-II)

Hb% toxicity is compared in 11 different periods of time. At day 7 of the treatment in Arm A, 1 patient reported with grade 2 (Hb% 9.5-7.5gm/dl) toxicity while 1 patient in Arm B showed grade 1 (Hb% 11.5-9.5 gm/dl) toxicity. At day 14 and 21 of the treatment only 1 patient in arm B had grade 1 toxicity. At 28 days after treatment in arm A, four patients showed grade 1 and one patient showed grade 2 toxicities. However, in Arm B only one patient had grade 1 toxicity. No statistically significant difference was observed between these two arms regarding Hb% toxicities. (Table-III)

Discussion

The mean age of the patients in arm A was 46.9 (SD ± 11.7) years and that of the arm B was 42.8 (SD ± 14.2) years. The age group distribution was almost identical which helped in minimizing bias. The other socio-demographic variables like socio-economic status, occupation or level education were not different across the two arms.

Headache and vomiting were the two main presenting complaints of the patients in both arms. More than 68% patients were suffering from glioblastoma multiforme and the rest were from anaplastic astrocytoma. All of the patients in Arm A tested positive for MGMT methylation test. Almost reverse findings was noted in arm B patients. Statistically this difference was highly significant (p<0.001).

Thrombocytopenia toxicity was also compared in several different periods of time starting from the beginning of the treatment to after 6 months of treatment completion. However, no differences of thrombocytopenia toxicities were statistically significant between these two arms (p>0.05).

Finally the treatment responses across the two arms were compared. In Arm A, 24 patients (80%) showed complete response and in Arm B, 20 patients (66.7%) showed complete response; partial responses were 2 (6.7%) and 4 (13.3%) in the two arms respectively. Progressive disease was noticed in 2 patients (6.7%) in each arm. Two patients (6.7%) in Arm A and 3 patients (10%) in Arm B came back with recurrence. One death (3.3%) was reported in conventional group i.e. in Arm B. Clinically this difference warrants much attention though statistical significance was not established in this regard.

References

1. Wen PY, Kesari S. Malignant Gliomas in Adult. NEJM. 2008; 3(5):492-7.
2. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, editors. SEER Cancer Statistics Review, 1975-2001. National Cancer Institute. Available from : http://seer.cancer. gov/csr/ 1975_2001/, 2004.
3. Mehta M, MichaelA, Vogelbaum, Chang S, Patel N. Neoplasms of the central nervous system. In : De Vita V Jr, Hellman S, Rosenberg S, editors Cancer: Principales and Practice of Oncology. Philadelphia: Lippincott Williams and Wilkins; 2011. pp.1700-49.
4. Barret A, Dobbs J, Morris S. Central nervous system:Practical Radiationtherapy Planning. Tom Roques. 2008; 225-30.
5. Ahmed R, Oborski mj, Hwang M, Lieberman FS, JM. Malignant gliomas: current perspectives in diagnosis, treatment, and early response assessment using advanced quantitative imaging methods. Cancer Manag Res. 2014; 6: 149–70.
6. Melean G, Sestini R, Ammannati F, Papi L. Genetic insights into familial tumors of nervous system. Am J Med Genet C Semin Med Genet. 2004; 15: (1):74-84.
7. Inskip PD, Linet MS , Heineman EF. Etiology of brain tumors in adults. Epidemiol Rev. 1995;17(2):382-414.
8. Galanis E, Bucker J. Chemotherapy for high grade gliomas. Br J Cancer. 2000; 82(8): 1371-80.
9. Curran WJ Jr, Scott CB, Horton J. Recursive partition-ing analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst. 1993; 5:85:704-10.
10. Friedman HS, McLendon RE, Kerby T, Dugan M, Binger SH, Henry AJ et al. DNA mismatch repair and osix alkylguanine DNA Alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. J Clin Oncol 1998; 16(12):3851-7.
11. Young WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD. A phase 11 study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 2000; 83: 588-93.
12. Stupp R, Dietrich PY, Ostermann Kraljevic S, Pica A, Maillard I, Maeder P et al: Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol. 2002; 20: 1375-82.
13. Choi JW, Lee MM, Kim IA, Kim JH, Choe G, Kim CY. The outcomes of concomitant chemoradiotherapy followed by adjuvant chemotherapy with temozolomide for newly diagnosed high grade gliomas : the preliminary results of single center prospective study. J Korean Neurosurg Soc. 2008. 44(4):222-7.
14. Walker MD, Alexander E Jr, Hunt WE, et al: Evaluation of BCNU and/or radreiotherapy in the treatment of anaplastic gliomas: A cooperative clinical trial. J Neurosurg. 1978; 49: 333-43.