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Original Study

A Retrospective Comparative Study of Concomitant Chemoradiotherapy followed by Adjuvant Temozolomide Versus Radiotherapy Alone In Newly Diagnosed Glioblastoma Multiforme – An Experience at Radium Institute, Patna Medical College and Hospital, India

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Abstract

Introduction

Glioblastoma Multiforme (WHO grade IV glioma) still remains a dreadful diagnosis in oncology with the median survival ranging between 12 to 17 months, despite the recent advances in its management[11,12] It is the most common malignant primary tumour in adults[13]. The standard of care is Maximal Safe Resection followed by Concomitant ChemoRadiotherapy[14].

Methods

During the period 2006 to 2010 at Radium Institute, Patna Medical College and Hospital (PMCH) in India, a study was conducted on 37 newly diagnosed GBM cases in which the control–arm (c–arm) received Conventional Radiotherapy (60Gy/30#) only whereas the study arm (s–arm) received Concomitant Chemoradiotherapy followed by Adjuvant Temozolomide.

Results

The median survival was 15.4 months in the s–arm as compared to 12.4 months in the c–arm. The OS showed a significant improvement with p–value of 0.05 and PFS also showed a benefit with a p–value of 0.005.

Conclusion

The results were encouraging with improvement in OS as well as PFS in the s–arm and were at par with the other similar studies conducted in different parts of the world.

Keywords

Concomitant Chemoradiotherapy, Temozolomide, Adjuvant, Glioblastoma Multiforme, GBM, WHO grade IV Glioma

دراسة استعادية مقارنة للمعالجة الكيميائية الإشعاعية المتزامنة والمتبوعة بالمساند تيموزولاميد مقابل المعاجلة الإشعاعية فقط في الحالات المشخصة حديثا لإصابتها بالورم الأرومي الدبقي متعدد الأشكال

– تجربة تم اجراؤها في معهد الراديوم – كلية الطب ومستشفى بانتا – الهند

مقدمة:

ما زال الورم الأرومي الدبقي متعدد الأشكال (الرتبة الرابعة بناء على تصنيف منظمة الصحة العالمية) يشكل تشخيصا مفزعاً في علم الأورام ، حيث يتراوح عمر البقاء الناصف للمصابين به ما بين 15 – 18 شهرا ، ويعتبر هذا الورم الدماغي الأولي الأكثر شيوعا بين البالغين .

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الوسائل

تم إجراء هذه الدراسة بمعهد الراديوم التابع لمستشفى و كلية الطب « باتنا» بالهند وذلك خلال الفترة ما بين 2006 إلى 2010 ، وأجريت على 37 حالة مشخصة حديثا لإصابتها بالورم الأرومي الدبقي متعدد الأشكال حيث خضعت المجموعة الضابطة (الشاهدة) الذراع الضابط إلى المعالجة الإشعاعية التقليدية فقط (جرعة قوامها 60 وحدة جراي/30/ جلسة) في حين خضعت مجموعة الدراسة (الذراع الدراسي) إلى المعالجة الإشعاعية والكيمائية المتزامنين تلاه علاجا كيميائيا بالمساعد أو المساند التيموزولاميد.

النتائج

كانت معايير الرعاية المتبعة هي القطع المأمون الأقصى والمتبوع بالمعالجة الكيميائية الإشعاعية المتزامنة ، وفي دراستنا هذه ، فإننا نتقارن بين المرضى الذي تلقوا المعالجة الكيمائية الإشعاعية المتزامنة والمتبوعة بالمساند تيموزولاميد مقابل المعالجة الإشعاعية فقط .

كان عمر البقاء الناصف (المتوسط) للمجموعة الدراسية (15.4) شهرا مقارنة (12.4) شهرا للمجموعة الضابطة ، وأظهرت البقيا العامة تحسنا ذو دلالة إحصائية معتد بها القيمة الإجمالية (P- value = 0.05) كما أظهرت قيمة البقيا بالمجموعة الضابطة (12.4) شهراً دون تطور للمرض فائدة ذات دلالة إحصائية قدرها (P- value = 0.005)

الخلاصة :

النتائج كانت مشجعة مع تحسن في قيمة البقيا العامة بالإضافة إلى قيمة البقيا دون تطور للمرض في المجموعة الخاضعة للدراسة ، وبذلك كانت متفقة مع نتائج الدراسات المماثلة الأخرى التي أجريت في أجزاء مختلفة من العالم .

الكلمات الرئيسية : المعالجة الإشعاعية الكيمائية المتزامنة ، التيموزولاميد ، المساند ، الورم الدبقي الأرومي متعدد الأشكال ، الورم الدبقي من الدرجة الرابعة تبعا لتصنيف منظمة الصحة العالمية .

Introduction

Glioblastoma multiforme continues to be one of the most challenging issues for the oncologist, even today in this advanced era of cancer treatment. Having undergone major changes in the treatment protocol over a period of several decades, a drug revolutionized the management of GBM, i.e., Temozolomide. Several studies in different parts of the world and also in India showed the improved outcomes by the use of TMZ along with RT in GBM. But there were no such study/data confirming the same in our part of the country where the resources are limited and understanding and affordability of the patients are also less. We have taken this opportunity to do the same study in our institute. Temozolomide (TMZ) is a non–classic alkylating agent, structurally and functionally similar to Dacarbazine. Because TMZ is lipophilic, it crosses the BBB and achieves 30–40% of those achieved in plasma.

Aim

The aim of this study was a) to report our institute's experience comparing the use of Temozolomide (TMZ) in concurrent and adjuvant settings along with radiotherapy versus conventional radiotherapy alone in newly diagnosed Glioblastoma Multiforme (GBM) cases. b) to determine the efficacy and safety profile of Temozolomide along with RT, and compare it with RT only in the treatment of newly diagnosed GBM cases.

Patients and Methods

During January 2006 to July 2010, 37 patients aged 11 to 70 years with newly diagnosed histologically confirmed glioblastoma (WHO grade IV astrocytoma) were selected from Radium Institute, Patna. Inclusion criteria were Karnofsky performance scale 60, adequate hematologic, renal and hepatic function. Out of 37 cases, 18 cases were assigned to the radiotherapy only group (c–arm) whereas 19 cases were assigned to radiotherapy plus TMZ group

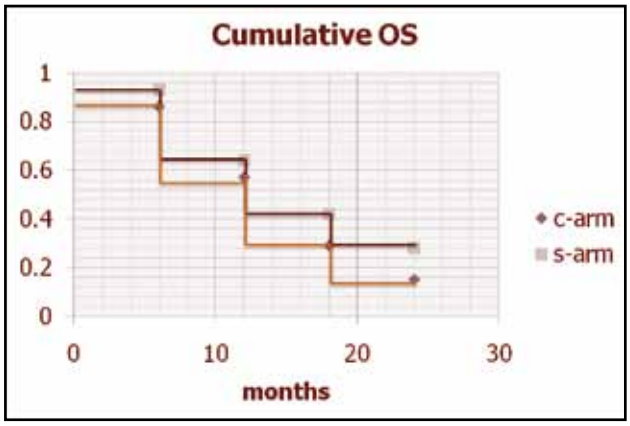

Figure 1: Kaplan Mayer curve for cumulative OS

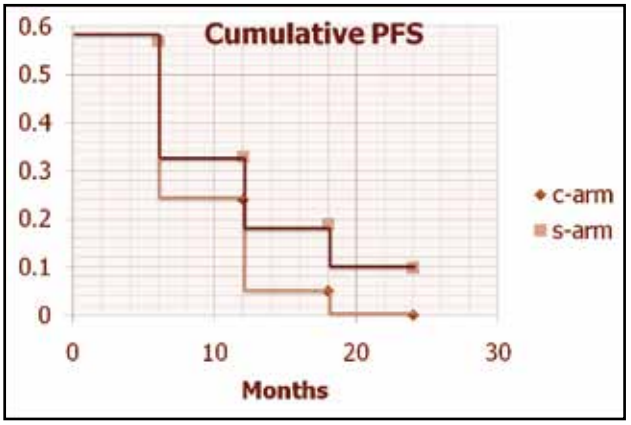

Figure 2: Kaplan Mayer curve for cumulative PFS

(s–arm). A total of 4 cases and 5 cases in control and study arms respectively were deleted from study due to: (a) KPS < 60, (b) Interruption due to toxicity of radiotherapy, (c) Interruption due to toxic effects of Temozolomide, (d) Discontinuation due to disease progression. Thus only 14 cases in each group (n=28) for detailed evaluation and final assessment were available. The cases were evaluated in terms of overall survival, progression free survival and toxicities.

Within six weeks after the histologic diagnosis of glioblastoma, the patients either received standard focal radiotherapy alone (c–arm) or standard radiotherapy plus concomitant daily TMZ, 75mg/M2 daily from day one (D1) until completion of radiotherapy but not beyond 49 days. After 4 weeks of gap adjuvant TMZ at a dose of 150mg/M2 from day 1 – day 5 of 1st cycle and 2nd cycle at 28 days of interval at a dose of 200mg/M2 from day 1 to day 5 (D1–D5) until completion of 6 cycles (s–arm). From day 6 (D–6) of each adjuvant Temozolomide therapy;

Variable	Radiotherapy (Control Arm) (n=14)	Radiotherapy +TMZ (Study Arm) (n=14)
Median Overall Survival (months)	12.4M (11.5–13.3)	15.4 months (14–17.6)
Overall Survival (%)		
At 6M	12 (85)	13(92 approx)
12 M	8(58 approx)	9(64)
18 M	4(28)	6(43)
24 M	2(14)	4(28)
Median Progression Free Survival (months)	9M (8.1–10.2)	12.5M (11.7–13.3)
6M	12(85)	12(85)
12 M	5(35)	7(50)
18 M	1(7)	4(28)
24 M	0(0)	2(14)

Table 1: Survival data for both the arms of study
Value (95% confidence interval)

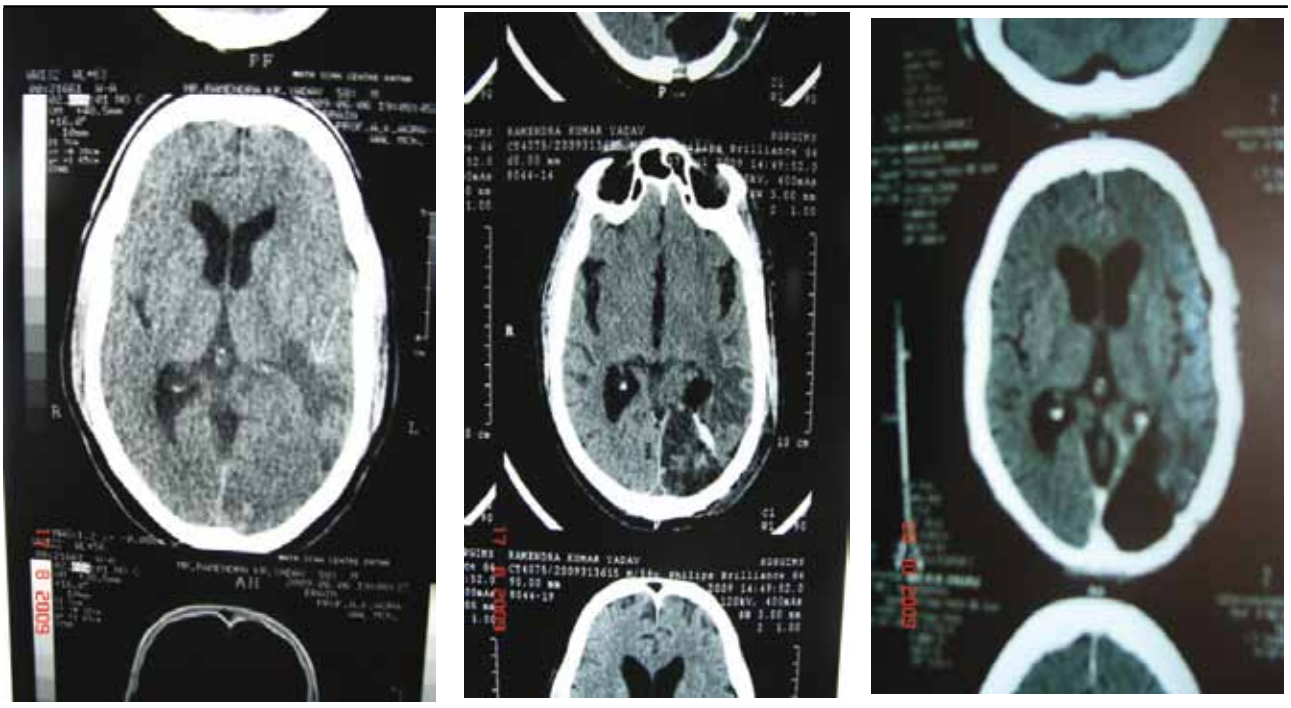

Figure 3: A series of CT scans– pre–operative, post–operative and post RT of a patient showing excellent response to the treatment of study

Toxic effect	C–Arm n=14 Entire period of treatment	S–Arm n=14 Entire study period
Leucopenia	0(0)	1(7)
Neutropenia	0(0)	1(7)
Thrombocytopenia	1(7)	2(14)
Anaemia	0	0
Any	1(7)	2(14)

Table 2. Haematological toxic effects (Gr. III or IV)

filgrastim 300 mcg subcutaneous given up to day 10.

- C–arm : Conventional Focal Radiotherapy
  - » Fractionated focal irradiation, 60 Gy/ 30 #, 5days a week for 6 wks
- S–arm: Conventional Focal Radiotherapy plus concomitant daily TMZ, 75mg/m2 from D1 until completion of RT but not beyond 49 days.
  - » After 4 weeks of gap, adjuvant TMZ ,150mg/m2,D1–D5 of 1st cycle
  - » Further after 4 weeks interval, 2nd cycle with TMZ,200mg/m2,D1–D5 until completion of 6 cycles

Radiotherapy consisted of fractionated focal irradiation at a dose of 2 Gy per fraction given once daily five days per week over a period of six weeks, for a total dose of 60 Gy to the Gross Tumor Volume with a 2–3 cm margin for the Clinical Target Volume. A boost was planned after 50Gy/25# with reduced margins. Radiotherapy was delivered by Co60 (Th780E) at the Radium Institute, Patna.

Oral trimethoprim–sulfamethoxazole (Bactrim DS tab bid) were given to patients in the "radiotherapy plus – temozolomide group" for prophylaxis against pneumocystis carinii pneumonia. Antiemetic prophylaxis with ondansetron 8mg thrice a day and dexamethasone daily before and during the course

of concomitant temozolomide was given and it was also required during the adjuvant five day course of temozolomide.

The patients were followed up once a month for six visits, then once in three months for 4 visits then six monthly. On each visit, we had a detailed clinical evaluation along with routine investigations and CT scan was done three monthly, to assess response during the course of treatment and thereafter to monitor for any progression. (Fig. 3)

Results

The median overall survival was 15.4 months in the study arm compared to 12.4 months in the control arm. This shows an absolute benefit of 3 months (Table 1). However, the median Progression free survival was 12.5 months and 9 months in the study arm and control arm respectively (Table 2). The Cumulative Survival was obtained in the form of Kaplan Mayer curves for OS and PFS both. The cumulative OS was 15% vs. 28% with a significant p–value of ≤0.05{X2=5.02;df=1} (Fig. 1). The cumulative PFS was 0% vs. 10% with highly significant p–value of ≤0.005{X2=10.52;df=1} (Fig. 2).

Entire study period = period from study entry to seven days after disease progression. The Haematological toxicities though more with s–arm, addition of suitable antibacterial drugs, filgrastim with best supportive and symptomatic care were easily manageable. (Table 2)

Conclusion

There was similarity between the baseline characteristics of the patients in the radiotherapy group (n–18) compared with those in the radiotherapy plus temozolomide group (n=19). At a median follow–up of 24 months, the study arm shows marked improvement in all the parameters:

- Median overall survival (in months) was 15.4 (mos.) vs. 12.4 (mos.) in control arm. Thus Median O.S. Benefit was 3 months in S–arm over C–arm. Cumulative OS = 15% vs. 28% (p–value ≤0.05, X^2= 5.02; df= 1), showing a significant p–value.
- Median progression free survival (P.F.S.) was 12.5 mos. (11.7–13.3) vs 9 mos. (8.1–10.2) in S–arm compared to C–arm. Again, an absolute benefit of 3.5 months was noted. Cumulative PFS = 0 vs 10% (p–value ≤0.005, X2= 10.52; df= 1), again with a significant p–value at the end of 24 months of follow up.
- The Haematological toxicities though more with S–arm, were quite manageable.

This leads us towards the following conclusions: a) Temozolomide along with Radiotherapy significantly prolongs overall survival, progression free survival with controlled haematological toxicities – entailing this to be the standard practice of newly diagnosed glioblastoma multiforme treatment. b) Despite the limitations and conventional resources, the results of our study are consistent with that of other similar studies conducted in our country as well as different parts of the world. c) This study further emphasizes that CCRT with TMZ followed by Adjuvant TMZ is the standard of care for newly diagnosed GBM patients in all settings with best possible results.

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