ADJUVANT TEMOZOLOMIDE EXTENSION BEYOND SIX MONTHS IN THE MANAGEMENT OF GLIOBLASTOMA MULTIFORM AND ITS EFFECT ON LOCAL RECCURENCE

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Introduction

Every year, approximately 100,000 people worldwide are diagnosed as having diffuse gliomas . Glioblastoma multiform (GBM), the most lethal glioma , accounts for 75% of all diffuse glioma diagnoses and has a median overall survival of 14–17 months. The standard initial approach for GBM is maximal safe surgical resection, which is followed by radiotherapy (RT) (60 Gray [Gy] over 6 weeks) with concomitant daily Temozolomide (TMZ) and a further 6 cycles of maintenance TMZ. Extending TMZ beyond 6 cycles has been shown to delay disease progression by some studies. Some guidelines suggest that this strategy is to be considered in patients with partial response or with continuing radiological improvement at the end of the 6th cycle. The residual disease is however expected in all patients with GBM and thus, it is hoped that additional cycles of TMZ will delay recurrence.

Aim of the work

This is a retrospective study to assess the impact of extended Temozolomide (TMZ) maintenance therapy (more than 6 cycles) in comparison with standard 6 cycles of TMZ maintenance therapy on overall survival (OS) and progression-free survival (PFS) in glioblastoma multiforme (GBM) patients.

Methods:

The study included 317 patients who were diagnosed with GBM and treated from Jan 2008 to Dec 2018 in Alexandria clinical oncology department (ACOD) and SUN Oncology Center in Alexandria.

Results

176 of the 317 patients with GBM received radiotherapy. 105 out of 176 patients who received radiotherapy also received adjuvant TMZ. Of the 105 patients who were treated with adjuvant TMZ, 33 received <6 cycles (TMZL), 41 received the standard 6 cycles (TMZS) and 31 received > 6 cycles (TMZE). TMZE had a significantly higher percentage of patients younger than 40 compared to TMZL and TMZS, 38.7 vs.12.1 vs. 17.1 respectively, p=0.023. The three groups were comparable regarding treatment parameters.69 patients out of the 105 who received adjuvant TMZ had a recurrence. The median PFS was 8.33 months in the TMZL group against, 13.53 and 26.10 months in (TMZS) and (TMZE) respectively (p=0.001). (Tables 1 figure 1) The median OS of TMZL was 12.53 compared to 18.63 in TMZS and 51.33 months in TMZE, p<0.001. (Tables 2 and figure 2)

Patients 40 years or younger had a median PFS of 16.1 months compared to 9.7 months in patients older than 40 years, p=0.028,and an OS of 51.3 vs 15.0 respectively, p<0.001. Patients who had radiotherapy, those with a performance status of 0-2 and those with a tumor size of <7cm in the greatest dimension also had better outcomes. However, In the multivariate analysis of the variables affecting PFS and OS, extended TMZ maintenance therapy beyond 6 cycles was the strongest independent factor.

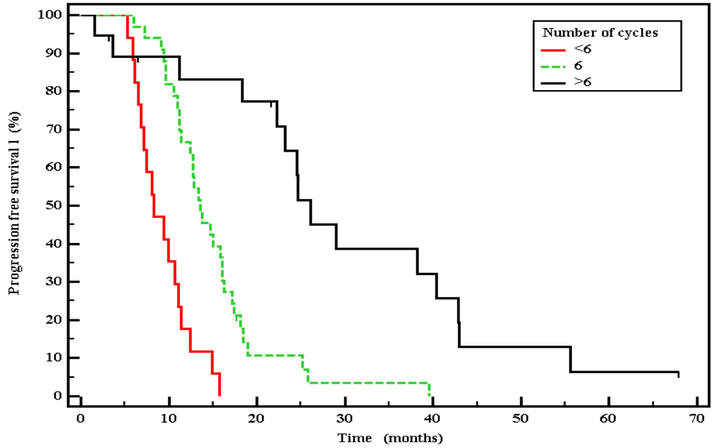

Figure (1): Kaplan-Meier curve for progression free survival with number of cycles for patients who received radiotherapy (n= 69)

Table (1): Progression free survival with number of cycles for patients who received radiotherapy (n= 69)

Number of cycles	Mean (months)	Median (months)	% 1year	% 3year	% 5year	Log rank	
						X^2	p
<6 (n =17)	9.255	8.330	17.6	–	–	43.8 23*	<0.00 1*
6 (n =33)	15.043	13.530	66.7	3.5	–		
>6(n =19)	30.213	26.100	83.2	38.6	6.4		

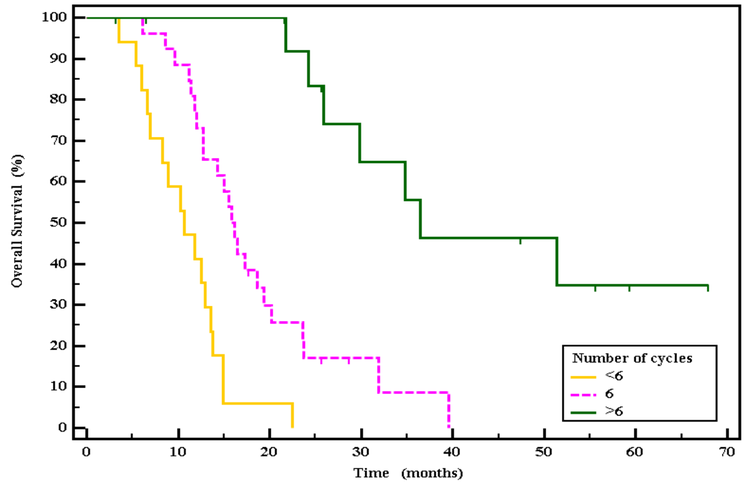

Figure (2):Kaplan-Meier curve for overall survival with number of cycles for patients who received radiotherapy (n= 105)

Table (2):Overall free survival with number of cycles for patients who received radiotherapy (n= 105)

Number of cycles	Mean (months)	Median (months)	% 1year	% 3year	% 5year	Log rank	
						X^2	p
<6 (n =33)	12.79	12.53	55.9	–	–	47.189 *	<0.001 *
6 (n =41)	23.59	18.63	81.8	23.2	–		
>6(n =31)	49.24	51.33	100.0	66.5	42.7		

Conclusions

Our study suggests that extending adjuvant TMZ beyond 6 cycles may significantly improve the PFS and OS in patients with GBM. Further randomized studies are needed to select patients who may benefit from an extended adjuvant TMZ regimen.