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The outcomes of concomitant hypofractionated simultaneous integrated boost intensity-modulated radiotherapy with temozolomide for newly diagnosed high grade gliomas

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SUMMARY

Purpose: Despite the multidisciplinary approach, within 2 cm of the primary site, 77% of Glioblastoma Multiforme (GBM) will recur. Thus, higher radiation dose seems reasonable to improve local control. We reported the preliminary results of the treatment with concomitant hypofractionated Simultaneous Integrated Boost Intensity-Modulated Radiotherapy (SIB-IMRT) plus Temozolomide (TMZ) followed by adjuvant TMZ therapy in patients with newly diagnosed GBM to determine the safety, tolerability, and efficacy.

Patients and Methods: Between January 2018 and February 2020, a total of 27 patients over the age of 18 years with newly diagnosed, histologically confirmed GBM were assigned to receive oral TMZ (75 mg/m^2/d × 7 d/wk for 6 weeks, from the first to the last day of RT) with fractionated RT (2.4 Gy, 2.2 Gy, and 2.0 Gy per fraction to PGTV, PCTV high risk, and PCTV low risk, 5 d/wk, for a total of 64.8 Gy, 59.4 Gy and 54 Gy, respectively) followed by TMZ monotherapy (150 mg/m^2/d to 200 mg/m^2/d × 5 days, every 28 days for six cycles) at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital. The primary end point was overall survival; secondary end points were progression-free survival, safety and tolerability. The date of this analysis is February 2021.

Results: At a median follow-up period of 20 months (range; 5-30 months), the median Progression-Free Survival (PFS) for all patients with GBM was 14 months, and the 2-year PFS rate was 19.2%. The median Overall Survival (OS) was 20 months and the 2-year OS rate was 40.8%. The mean age was 50.2 years (standard deviation ± 9.7284), and 44.4% of patients had undergone biopsy only. There was no mortality caused by drug toxicity. Patients younger than 50 years old and patients who underwent debulking surgery had the best survival outcome.

Conclusion: The addition of TMZ to hypofractionated SIB-IMRT followed by adjuvant TMZ was well tolerated and has shown promising activity in the treatment of newly diagnosed GBM. Further investigation is warranted.

Key words: glioblastoma multiforme, hypofractionated Simultaneous Integrated Boost Intensity-Modulated Radiotherapy (SIB-IMRT), temozolomid

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INTRODUCTION

Patients with glioblastoma have a highly malignant disease with poor prognosis [1-3]. Primary brain tumours has an incidence of about 5 per 100,000 persons [1]. In adults, the most common histologies are grade 3 Anaplastic Astrocytoma (AA) and grade 4 Glioblastoma Multiforme (GBM) [4,5].

The standard management of GBM involves surgical resection to the extent that is safely feasible [6,7], followed by radiotherapy (60 Gy with 1.8-2.0 Gy per fraction, over a period of 6 weeks) [2] with concomitant and adjuvant Temozolomide (TMZ) chemotherapy [8,9].

Despite this multidisciplinary approach, within 2 cm of the primary site, 77% of GBM will recur [10]. Due to its higher rate of recurrence, a newer approach to treatment of GBM such as photothermal therapy is emerging. Photothermal therapy uses heat to destruct the tumour. Heat therapy is a non-chemical method of treatment, it bypasses the heterogeneity limitations of GBM, overcomes the conventional mechanisms of drug resistance and side effects on normal tissues. However, its advance is hindered by the unique features of this tumour [11].

Most of the cases (72%) will recur in field of radiotherapy [6,12-15]. which could result from insufficient therapeutic doses rather than insufficient therapeutic target volume [16]. Thus, higher radiation dose seems reasonable to improve local control with the hope of improving survival [17]. Either hyperfractionation, hypofractionated radiotherapy or increasing the total dose could contribute to dose escalation [2].

However, previous studies [18-20] did not show a significantly increased survival by increased total dose with hyperfractionation and conventional fractionation. There were many trials exploring the hypofractionated radiotherapy for glioma. In the early stages, some scholars applied the traditional radiotherapy technique and increased the dose of single fractionation, they did not show a clear survival benefit [21-23]. With the advent of precision radiotherapy, especially the clinical application of Simultaneous Integrated Boost Intensity Modulated Radiation Therapy (SIB IMRT), the dose in tumour regions can be precisely increased without increasing the dose in normal tissues at the same time, and the Biologically Effective Dose (BED) on tumour could be increased [24-27]. Studies with a larger

single fractionated dose showed increased efficacy, as well as a high incidence of radiation necrosis [25-27]. Therefore, the appropriate single fractionated dose still required further studies.

On the basis of this evidence, we initiated this study to investigate the safety, tolerability, and survival of concomitant hypofractionated Simultaneous Integrated Boost Intensity Modulated Radiation Therapy (SIB IMRT) plus TMZ therapy followed by adjuvant TMZ therapy in patients with newly diagnosed GBM.

PATIENTS AND METHODS

Patients

Between January 2018 and February 2020, 32 patients over the age of 18 years with newly diagnosed, histologically confirmed Glioblastoma Multiform (GBM), were the subjects of this study, of which 27 were assessable for response at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital. Five patients were ineligible, not treated, or inadequately treated: reasons included treatment refusal (n=2) and hepatic insufficiency (n=3). Patients were required to have a Karnofsky Performance Status (KPS) of ≥ 70 and adequate hematologic, renal, and hepatic functions, defined as absolute neutrophil count ≥ 1.5×10^9 cells per liter; platelet count ≥ 100×10^9 cells per liter; hemoglobin more than 90 g/L; serum creatinine and total serum bilirubin ≤ 1.5 times the upper limit of normal; aspartate aminotransferase or alanine aminotransferase less than 2.5 times the upper limit of normal; and alkaline phosphatase less than 2.5 times the upper limit of normal. Study enrollment had to be within six weeks from diagnostic biopsy or resection. Eligible patients were also required to have no other severe underlying disease (including chronic hepatitis B or C infection). Exclusion criteria included any medical condition that could interfere with the oral administration of temozolomide or any previous or concurrent malignancies at other sites.

This is a prospective study, and approval was obtained from the Tanta University ethics committee.

Study design and treatment

Within six weeks after the histologic diagnosis of GBM, we assigned eligible patients to receive temozolomide (marketed as Temodal) at a dose of 75 mg per square meter per day, given 7 days per week from the first day of radiotherapy until the last day of radiotherapy, in a fasting state, 1 hour before RT, and in the morning on days without RT. Concomitant focal hypofractionated simultaneous integrated boost intensity modulated radiation therapy (SIB IMRT) was delivered once daily 2.4 Gy, 2.2 Gy, and 2.0 Gy per fraction to PGTV, PCTV high risk, and PCTV low risk, 5 d/wk, for a total of 64.8 Gy, 59.4 Gy and 54 Gy, respectively in 27 fractions over 6 weeks. The planning goal was achieving dose encompassing at least 95% of the PTV, and no more than 10% of the PTV received more than 110% of the prescribed dose. Adequate immobilization masks were required to ensure reproducibility. Treatment using 6 MV photon beams was delivered with an MLC-equipped megavoltage linear accelerator. Treatment volumes were determined on the basis of preoperative gadolinium-enhanced Magnetic Resonance Imaging (MRI) of the brain and contrast-enhanced Computed Tomography (CT) with 3 mm slice thickness. The CT images were then transferred to the treatment planning (eclipse system). Treatment volume generally included; the Gross Tumour Volume (GTV) which was defined as the contrast-enhancing lesion, The Clinical Target Volume (CTV) high risk which was defined as GTV plus a, 1 cm-2 cm margin including surrounding edema, CTV low risk which was defined as CTV high risk plus 1 cm-2 cm margin and the Planning Target Volume (PTV), which was defined as the PCTV low risk plus a 0.5 cm margin. The margin could be modified depending on the location of the tumour if there were Organs at Risk (OARs), as lens, optic chiasm, optic nerves, hippocampus and the brain stem. The maximum dose constraints for the brain stem, optic nerves and chiasm are 54 Gy, the maximum for lenses is 5 Gy, the maximum dose for hippocampus is less than 24 Gy, and the mean dose was less than 12 Gy. After a 4-week break, patients were then to receive up to six cycles of adjuvant temozolomide according to the standard 5-day schedule every 28 days. The dose was 150 mg per square meter for the first cycle and was increased to 200 mg per square meter beginning with the second cycle, so long as there were no hematologic toxic effects. Prophylactic antiemetics were used only as required during concomitant hypofractionated Simultaneous Integrated Boost Intensity Modulated Radiation Therapy (SIB IMRT) plus temozolomide therapy. Prophylactic antiemetics, including metoclopramide or 5-hydroxytryptamine-3 antagonists, were routinely prescribed once a day before adjuvant temozolomide. Anticonvulsants and corticosteroids were administered as needed.

Surveillance and follow-up

The baseline examination included a complete medical history, physical examination, determination of performance status, hematology and clinical chemistry assessments, and gadolinium-enhanced MRI or contrast-enhanced CT of the brain. During hypofractionated Simultaneous Integrated Boost-Intensity-Modulated Radiation Therapy (SIB-IMRT) with temozolomide, complete blood counts were checked weekly, and blood chemistry was checked monthly. During adjuvant temozolomide therapy, patients underwent a monthly clinical evaluation and a comprehensive evaluation at the end of cycles 3 and 6. Tumour progression was defined according to the modified WHO criteria as an increase in tumour size by 25 percent, the appearance of new lesions, or an increased need for corticosteroids [28]. When there was tumour progression, patients were treated at the investigator's discretion, and the type of second-line therapy was recorded. Toxicity grading was based on the common terminology criteria for adverse event (NCI-CTC, version 3.0) [29], with a score of 1 indicating mild adverse effects, a score of 2 moderate adverse effects, a score of 3 severe adverse effects, and a score of 4 life-threatening adverse effects.

End points

The primary end point was overall survival; secondary end points were progression-free survival, and safety. Safety and toxicity are reported for all treated patients.

Statistical analysis

The date of this analysis was February 2021. Toxic effects are reported separately for the radiotherapy period, defined as extending from day 1 of radiotherapy until 28 days after the last day of radiotherapy, or until the first day of adjuvant temozolomide therapy. The adjuvant-therapy period was defined as extending from the first day of adjuvant temozolomide therapy until 35 days after day 1 of the last cycle of temozolomide. Findings with respect to the quality of life are not reported here.

Overall survival was calculated from the time of study entry until death or last follow-up according to the Kaplan-Meier method [30] with SPSS (Statistical package) (version 21). Mean and standard deviation were estimates of quantitative data. Overall survival and progression-free survival were compared by the Kaplan-Meier method [30] with statistical significance assessed by the log-rank test. All P-values were two-tailed; a value of ≤ 0.05 was considered significant.

RESULTS

Patient characteristics

Patients ≥ 18 years of age with newly diagnosed and histologically proven GBM were eligible for this study. Patient demographics and baseline disease characteristics for the eligible 27 patients are listed in table 1. The mean age was 50.2 ± 9.7 years old, (range; 21-71 years old). The majority of patients had a Karnofsky Performance Status (KPS) of ≥ 80. About 44% of the patients underwent biopsy only, 22.2% underwent gross total resection, and 18.5% underwent subtotal resection, however, immediate postoperative imaging was not performed in all patients. Histopathological slide revisions were confirmed the diagnosis of glioblastoma multiform in all of the patients. The mean time from diagnosis to the start of therapy with RT plus temozolomide was 2.7 weeks, standard deviation ± 0.9842, (range, 1-5 weeks).

Tab. 1. Demographic characteristics of the 27 patients with GBM at baseline

Characteristic	Radiotherapy plus temozolomide No. of patients (%)
Age (years)	
Mean	50.2
Range	21-71
<50 years	11 (40.7)
≥ 50 years	16 (59.3)
Sex	
Male	15 (55.6)
Female	12 (44.4)
Male to female ratio	1.25:1
Karnofsky performance status at diagnosis	
≥ 80	25 (92.6)
<80	2 (7.4)
Karnofsky performance status after CCRT	
≥ 80	22 (81.5)
<80	5 (18.5)
Extent of surgery	
Gross total removal	6 (22.2)
Near-total removal	2 (7.4)
Subtotal removal	5 (18.5)
Partial removal	2 (7.4)
Biopsy	12 (44.4)
Time from diagnosis to radiotherapy (weeks)	
Mean	2.7407
Standard deviation	±0.9842
Median	3
Range	1-5
<2	5 (18.5)
2-4	20 (74.1)
>4	2 (7.4)
Corticosteroid therapy	
During CCRT	
Yes	12 (44.4)
No	15 (55.6)
During chemotherapy	
Yes	11 (40.7)
No	16 (59.3)

Table 2 summarizes the details of treatment. Among the 27 patients who were assigned to receive concomitant hypofractionated simultaneous integrated boost intensity-modulated radiotherapy plus temozolomide, 17 (63%) completed both radiotherapy and temozolomide as planned. Ten patients (37%) prematurely discontinued adjuvant temozolomide because of toxic effects (in 3 patients), disease progression (in 5 patients), or other reasons (in 2 patients). The majority of patients completed their hypofractionated simultaneous integrated boost intensity-modulated radiotherapy within the prescribed 6 weeks (42 ± 3 days). Unplanned interruptions in hypofractionated simultaneous integrated boost intensity-modulated radiotherapy was usually brief (median, four days) and interruptions due to the toxicity of therapy occurred in only 18.5% of patients. In 9 patients, the duration of hypofractionated simultaneous integrated boost intensity-modulated radiotherapy was more than 6.5 weeks (maximum, 56 days), and in 5 of these patients RT was delayed because of grade 3 or 4 hematologic toxicities (leukocytopenia and thrombocytopenia). The other reasons were mainly administrative (e.g., holidays, radiotherapy equipment maintenance, or technical problems). After hypofractionated simultaneous integrated boost intensity-modulated radiotherapy plus temozolomide, patients started adjuvant temozolomide and received a mean of 5.1 cycles (range, 1-6); 63% of patients completed 6 cycles. The median time from the completion of RT and the beginning of adjuvant temozolomide treatment was 29 days (range, 28 to 63 days). The main reason for not beginning or not completing adjuvant temozolomide therapy was disease progression (Adjuvant chemotherapy was discontinued early because of progressive disease in 5 patients (18.5%). Only 5 patients discontinued adjuvant temozolomide because of toxic effects. Beginning with cycle 2, the dose of temozolomide was increased to 200 mg per square meter in 70.4% of patients. Seventeen patients (63%) received all concomitant and adjuvant temozolomide as planned in the protocol. The response rate, including complete remission and partial remission, was 55.6%.

Safety and tolerability

We analyzed adverse events separately during hypofractionated simultaneous integrated boost intensity-modulated radiotherapy with concomitant temozolomide, the adjuvant-therapy period,

Tab. 2. Disposition of patients and intensity of treatment in the 27 patients with GBM

Variable	Radiotherapy plus temozolomide
Concomitant chemoradiotherapy (CCRT)	
Duration of CCRT (weeks)	
Mean	5.7
Standard deviation	± 0.963
Range	4.5-8
Radiotherapy Dose (Gy)	
Mean	60.037
Standard deviation	± 4.4418
Range	45-64
Adjuvant chemotherapy	
Duration of adjuvant chemotherapy (weeks)	
Mean	20.6
Standard deviation	± 10.375
Range	1-26
Cycles of temozolomide	
Median	6
Mean	5.1
Standard deviation	± 1.517
Range	1-6
Dose of temozolomide (mg)	
<150	10 (37)
≥ 150	17 (63)
Response	
Complete remission	6 (22.2)
Partial remission	9 (33.4)
Stable disease	6 (22.2)
Progressive disease	6 (22.2)

and the entire study period (from study entry until disease progression or last follow-up).

Hematologic toxicity and infection

Concomitant phase of treatment: During the concomitant hypofractionated simultaneous integrated boost intensity-modulated radiotherapy plus temozolomide phase, grade 3 or 4 neutropenia occurred in 2 patients (7.4%) (Table 3), and grade 3 or 4 thrombocytopenia occurred in 2 patients (7.4%), with 1 patient experiencing platelet counts of less than 10,000 cells per cubic millimeter. Grade 3 or 4 lymphocytopenia occurred in 3 patients (11.1%).

Two patients had infections that required hospitalization and treatment interruption. Analysis indicated that 1 of the 2 patients developed pneumonia. This patient was receiving corticosteroids and experienced grade 4 neutropenia and lymphocytopenia at the time of infection. One patient required surgical revision of a scar infection and osteomyelitis 3 weeks after start of RT. However, this patient's blood counts were within normal limits during treatment.

Adjuvant temozolomide: During the adjuvant temozolomide phase, grade 3 or 4 neutropenia or thrombocytopenia occurred in 7.4% and 18.5% of patients, respectively. Five patients required a dose reduction or delay because of grade 3 or 4 thrombocytopenia.

Non-hematologic toxicities

Non-hematologic toxicities were mild to moderate (Table 4). During the CCRT phase, prophylactic antiemetics were required in 59.3% of patients; however, only 7 patients (25.9%) received antiemetics for longer than the first week of the concomitant treatment. During the adjuvant temozolomide phase, 33.3% of patients required antiemetic therapy. One patient experienced a treatment-induced rash that resulted in early discontinuation of temozolomide after 7 days of CCRT. Moderate to severe fatigue was reported in 5 patients during the CCRT phase (grade 3; one patient) and in 5 patients during the adjuvant temozolomide phase (grade 3; one patient).

The short duration of follow-up precludes definitive assessment of late radiation toxicity; only 9 patients were alive with a follow-up longer than 24 months. However, signs of leukoencephalopathy, without evident clinical impairment, were apparent on MRI in all of these patients. One patient developed intracranial hypertension, refractory seizures, and loss of vision 25 months after beginning RT. The loss of vision may in part be due to prior RT. Subsequent work-up indicated a spinal dissemination of the disease with positive CSF cytology and no evidence of local recurrence. A second patient developed neurologic deterioration with progressive short-term memory loss and hemiplegia 17 months after beginning RT. At 26 months, this patient was still alive without evidence of tumor progression. The remaining patients with follow-up longer than 24 months are doing well without any clinical signs of neurologic impairment.

Thromboembolic events occurred in 3 patients (11.1%). Two patients died of cerebral haemorrhage in the absence of a coagulation disorder or thrombocytopenia.

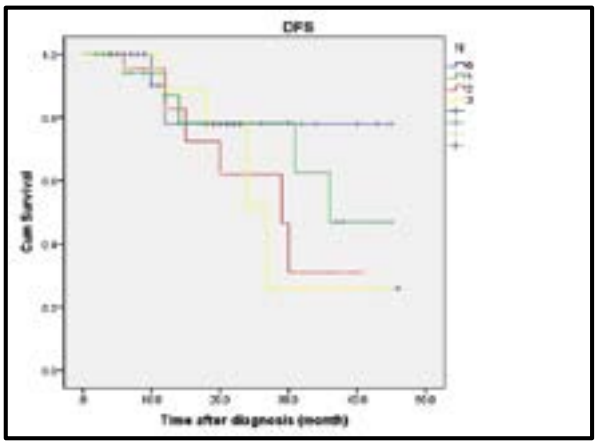

Fig. 1. Overall Survival of patients with glioblastoma (n=27)

Tab. 3. Hematologic toxicities and infection in the 27 patients with GM

Adverse Event	RT with concomitant TMZ				Adjuvant TMZ			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Anemia	1	3.7	0	0	1	3.7	0	0
Neutropenia	1	3.7	1	3.7	1	3.7	1	3.7
Thrombocytopenia	1	3.7	1	3.7	2	7.4	3	11.1
Lymphocytopenia	2	7.4	1	3.7	3	11.1	3	11.1
Infection	1	3.7	1	3.7	0	0	0	0

Tab. 4. Non-hematologic toxicities in the 27 patients with GM

Adverse Event	RT with concomitant TMZ						Adjuvant TMZ					
	Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nausea/vomiting	6	22.2	1	3.7	0	0	7	25.9	2	7.4	0	0
Rash	0	0	1	3.7	0	0	0	0	0	0	0	0
Fatigue	4	14.8	1	3.7	0	0	4	14.8	1	3.7	0	0

Tab. 5. Overall Survival and progression-free survival of all patients with GBM (n=27)

Variable	Survival
Overall Survival (months)	
Median	20.00 months
95% confidence interval	(9.08-30.90) months
12- month	75.50%
24- month	40.80%
Progression-free survival (months)	
Median	14.00 months
95% confidence interval	(7.76-20.24) months
12- month	51.20%
24- month	19.20%

Survival

At the time of this analysis, 19 patients had died. The median duration of follow-up was 20 months, (range; 5-30 months). On the basis of Kaplan-Meier estimates, the median overall survival for the all patients with GBM (n=27) was 20 months (95% confidence interval, 9.08-30.90) (Table 5). The one-year and two-year overall survival rates were 75.5% and 40.8% respectively (Figure 1).

The median progression-free survival was 14 months (95% confidence interval, 7.76-20.24) (Table 5). The six-month, 1-year and 2-year progression-free survival rate were 74.1%, 51.2% and 19.2% respectively (Figure 2).

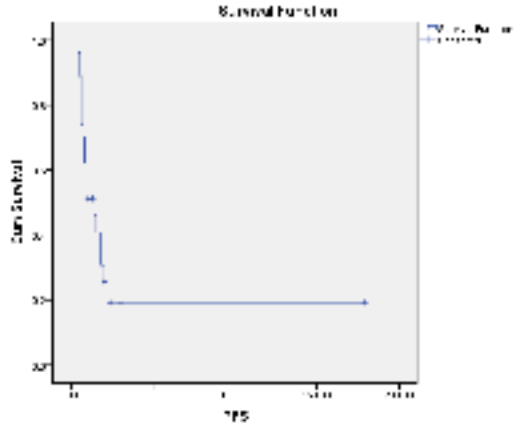

Fig. 2. Progression-free survival of patients with glioblastoma (n =27)

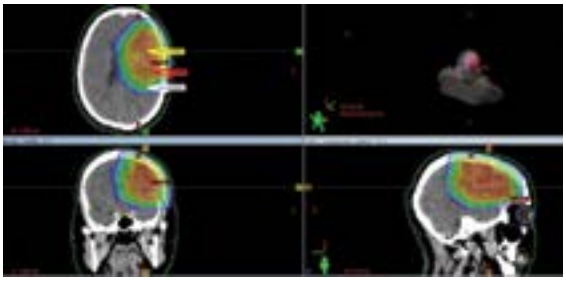

Fig. 3. The target volume delineation and isodose distribution of a representative patient who received hypofractionated SIB-IMRT. Isodose distribution in CT, showing the target volumes receiving64.8 Gy (yellow), 59.4 Gy (red), or 54 Gy (white)

Prognostic factors

We analysed the median overall survival and survival rates of the eligible patient populations in relation to prognostic indicators. In patients younger than 50 years old, the median survival was not reached at 24 months, with 66.7% of these patients still alive at 24 months. In patients ≥ 50 years old, the 24 months overall survival was only 35.7% months (P=0.005). The prognosis by surgical respectability was also analysed in these eligible patients. Patients who underwent gross total resection, near-total removal and subtotal resection had 24 months overall survival of 57%. However, for patients who underwent partial removal or biopsy, the 24 months overall survival was 26.8% (P=0.0017).

Survival according to other possible prognostic factors were included, Karnofsky Performance Status (KPS) (P=<0.001), and sex (P=0.495), were also analysed.

Treatment after Disease Progression: If disease progression occurred, further treatment was at the physician's discretion. At the time of progression, part of the progressed patients underwent a second surgery, and the remaining patients received salvage chemotherapy. The type of chemotherapy and response to salvage chemotherapy was not recorded as part of our study.

DISCUSSION

Despite surgery and RT with or without adjuvant chemotherapy, GBM remains an almost uniformly fatal disease characterized by a rapid and devastating clinical course [31]. The value of RT was established in randomized trials in the late 1970s and is now considered the standard of care [8, 32-34].

The concept of RT concomitantly with chemotherapy has been explored by using several agents with radiosensitizing properties, such as topotecan and tirapazamine. A RTOG phase I trial, in which 47 GBM patients were treated with concomitant RT plus topotecan, reported a median survival of 9.7 months [35]. Similarly, 124 GBM patients treated with concomitant RT plus tirapazamine, a hypoxia-selective cytotoxin, had a median survival of approximately 10 months [36]. Furthermore, Kleinberg, et al. [37] reported a median survival of 12.8 months for patients treated with concomitant RT plus cisplatin and BCNU.

Temozolomide, is a second-generation, oral alkylating agent, that has demonstrated antitumor activity as a single agent in the treatment of recurrent glioma [38-44]. In 2002, a promising regimen of concomitant RT plus TMZ followed by adjuvant TMZ therapy for patients with GBM was reported [45]. At present concomitant RT plus TMZ followed by adjuvant TMZ therapy is widely accepted as the current standard care for patients with glioblastoma [46-55].

Because most recurrences in malignant gliomas occur within 2 cm of the previous resection [12-15], which could be due to insufficient therapeutic doses, high-dose radiation therapy has been investigated in these patients to improve local control with the hope of improving survival. Previous trials have investigated the therapeutic ratio of hypofractionated SIB-IMRT combined with TMZ [8, 23, 25, 56].

With reference to these studies, we proceeded to apply this protocol, to patients with GBM from 2018 at our Clinical Oncology Department, Tanta University Hospital. Survival results in our study are encouraging. Indeed, the median PFS time of 14 months, the 2-year PFS rate of 19.2%, the median overall survival of 20 months and the 2-year overall survival rate of 40.8% for the 27 patients with glioblastoma in our series treated with concomitant hypofractionated SIB-IMRT plus TMZ followed by adjuvant TMZ therapy compares favourably with the other previous reported protocols.

Some reports of concomitant hypofractionated SIB-IMRT plus TMZ followed by adjuvant TMZ therapy for GBM were published. In 2019, the efficacy of postoperative TMZ radiochemotherapy in GBM was reported [8]. According to that report, median PFS time was 15 months for primary glioblastoma, treated with concomitant hypofractionated SIB-IMRT plus TMZ followed by adjuvant TMZ therapy. That study also reported that the median overall survival time for patients with glioblastoma was 21 months. Other prospective studies of concomitant hypofractionated SIB-IMRT plus TMZ followed by adjuvant TMZ therapy was reported in 2009-2011 [23,24,56] proving that this protocol is more effective than standard RT plus TMZ followed by adjuvant TMZ therapy in patients with newly diagnosed glioblastoma [46].

There is no definite consensus about the standard regimen for hypofractionated SIB-IMRT. For example, in our study, concomitant focal RT was delivered once daily 2.4 Gy, 2.2 Gy, and 2.0 Gy per fraction to PGTV, PCTV1, and PCTV2, 5 d/wk, for a total of 64 Gy, 60 Gy and 54 Gy, respectively over 6 weeks. However, in Sultanem, et al. [57] preliminary results of a prospective trial of use of hypofractionated intensity-modulated irradiation in the treatment of glioblastoma multiforme to treat 25 patients with GBM was published in 2004 [57]. A total of 60 Gy over 20 daily fractions of 3 Gy each were applied to the GTV, and the PTV received a minimum of 40 Gy over 20 fractions of 2 Gy each at its periphery. This study concluded that hypofractionated SIB-IMRT did not prolong the survival of patients with GBM [The median OS was 9.5 months, and the median PFS was 5.2 months]. Therefore, it is essential to verify the role of optimum hypofractionated SIB-IMRT plus TMZ regimen in the treatment GBM.

Since the above-mentioned study of Sultanem, et al. [57], there have been many clinical studies of the treatment of GM with SIB-IMRT combined with TMZ in adults [23,25,46,57,58]. Panet-Raymond, et al. [23] published a study to treat 35 patients with GBM with a total of 60 Gy. During a 4-week period, over 20 daily fractions of 3 Gy each were applied to the GTV, and the PTV received a minimum of 40 Gy over 20 fractions of 2 Gy each at its periphery. The median survival was 14.4 months, and the median disease-free survival was 7.7 months. The most common acute toxicity was moderate fatigue. No patient developed late toxicity. Another randomized prospective study of concomitant SIB-IMRT plus TMZ was reported in 2018 proving that this protocol is more effective than Conventionally Fractionated Radiation Therapy (CRT) in 83 patients with newly diagnosed glioblastoma [58]. This randomized study compared concomitant Conventionally Fractionated Radiation Therapy (CRT) plus TMZ with SIB-IMRT combined with TMZ in patients with newly diagnosed glioblastoma. During a 4-week period, doses of 60 Gy and 50 Gy were delivered in 20 fractions prescribed to the CTV60 and CTV50, respectively in SIB-IMRT combined with TMZ arm. In concomitant Conventionally Fractionated Radiation Therapy (CRT) plus TMZ arm, during a 5-week period, doses of 50 Gy in 25 fractions were delivered to CTV50 and followed by a 10 Gy boost over 5 fractions prescribed to the CTV60. It reported that the median OS for all studied patients was 23.4 months, the median overall survival time for patients with glioblastoma was not significantly different between the two arms, with a median OS of 18.07 and 25.18 months (p=0.3). The median PFS for all studied patients was 13.5 months. One patient (1.2%) had documented radionecrosis [58]. Another multicenter phase II study by the brain study Group of the Italian Association of Radiation Oncology (AIRO) explored the therapeutic ratio of SIB-IMRT combined with TMZ in 24 patients with newly diagnosed glioblastoma. During a 3-week period, doses of 55.2 Gy and 67.5 Gy in 15 fractions were delivered to SIB volume. The median OS and the median PFS were of 15.1 months and 8.6 months, espectively. One patient (4.2%) developed radionecrosis of the brain parenchyma [59].

Zhong, et al. [8] carried out a study to observe the efficacy of SIB-IMRT combined with TMZ in 80 patients with GBM. Daily doses of 2.4 Gy, 2.2 Gy, and 2.0 Gy were delivered to PGTV, PCTV1, and PCTV2 with a total dose of 64 Gy, 60 Gy and 54 Gy, respectively, in 27 fractions over 6 weeks. The median OS and PFS rates were 21 months and 15 months, respectively. The 1, 2 and 3 year rates of PFS among the whole group were 56.0, 27.6, and 19.5%, respectively. The 1, 2, 3, and 5-year rates of OS were 77.6, 41.6, 32.8, and 13.4%, respectively. The most common acute toxicities were nausea, fatigue, headache and hematologic toxicities. The most common late adverse effects were cognitive disturbances [8].

This trial had reported good outcomes, and our present results for patients with GM are also favourable, with tolerable toxicity. In our study the median PFS time was 14 months, and the median overall survival was 20 months for the 27 patients with GM treated with concomitant SIB-IMRT plus TMZ followed

by adjuvant TMZ therapy. Our results are compared favourably with most of these reports, confirming that concomitant SIB-IMRT plus TMZ followed by adjuvant TMZ therapy offers good clinical outcomes in the treatment of GM.

In this study, we examined the safety and efficacy of concomitant hypo fractionated SIB-IMRT plus TMZ followed by adjuvant TMZ therapy in patients with newly diagnosed GM. Our study confirms the overall excellent tolerability of hypo fractionated SIB-IMRT plus TMZ as was the case in other studies [23, 25, 56-59]. In our study, myelosuppression, a well-documented side effect of therapy in particular thrombocytopenia, was the predominant toxicity. Hematologic toxicity during the adjuvant temozolomide treatment phase was in agreement with many of the previous reports [23, 25, 56-59].

In this study, lymphocytopenia is often observed with TMZ treatment but may, in part, be due to the frequent administration of corticosteroids as was described in another phase I trial [60]. Although lymphocytopenia occurs frequently, it is not typically associated with clinical sequelae. However, one of the 27 patients we treated with concomitant hypo fractionated SIB-IMRT plus TMZ therapy developed pneumonia. The frequency of opportunistic infections in a similar patient population treated with RT alone is unknown.

Nausea and vomiting, the most frequently reported non-hematologic adverse events, were also mild to moderate and could be readily controlled with the administration of standard antiemetics. Non-hematologic toxicity observed with temozolomide treatment was in agreement with the report published by Stupp et al [45].

Late toxicity resulting from exposure to alkylating agents or combined modality treatment remains a concern. Concomitant hypo fractionated SIB-IMRT plus TMZ therapy did not increase late toxicities associated with RT during our follow-up period; however, follow-up remains too short to make any conclusions with regard to late toxicities resulting from treatment with Concomitant hypo fractionated SIB-IMRT plus TMZ.

Subanalyses performed to determine the existence of prognostic factors in the patient population under evaluation revealed that baseline KPS was an important prognostic factor that correlated meaningfully with median survival ($p \leq 0.001$), this was in agreement with the report published by Zhong, et al. [8] and Scoccianti, et al. [61]. Age (p=0.005) and extent of resection (p=0.0017) were also important significant prognostic factors for GBM. As expected, younger patients and patients with a gross complete or subtotal resection had substantially better survival rates than patients who had a biopsy only. These prognostic factors observed in our patient population under evaluation were in agreement with many of the previous reports [1, 2, 8, 61-63].

CONCLUSION

In conclusion, this is the first report of results of concomitant hypofractionated SIB-IMRT plus TMZ followed by adjuvant TMZ therapy in the treatment of GM in Clinical Oncology Department, Tanta University Hospital, Faculty of Medicine, Tanta University, Egypt. This study demonstrated concomitant hypo fractionated SIB-IMRT plus TMZ followed by adjuvant TMZ therapy, is a promising regimen for patients with GM and we propose concomitant hypofractionated SIB-IMRT plus TMZ followed by adjuvant TMZ therapy as an alternative approach with tolerable toxicities for patients with glioblastoma, nevertheless, the challenge remains to improve clinical outcomes further. To confirm this, a multicenter, meta-analysis and a randomized trial with a large number of patients are required in the near future. Many questions remain unanswered regarding the applications of this regimen to lower grade gliomas and the optimal combination of hypofractionated SIB-IMRT and temozolomide.

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