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Conformal Radiation therapy with Concurrent Gemcitabine in treating Patients with Glioblastoma Multiforme

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Abstract

Purpose
The aim of this work was to access the safety and efficacy of Gemcitabine as a radiosensitizer for newly diagnosed glioblastoma multiform patients.
Methods
Patients with newly diagnosed histologically proven GBM with evaluable and/or measurable disease after surgery were eligible for the study. Radiotherapy at a dose of 2.0 Gy per fraction given once daily, 5 days/week, over a period of 6 weeks, for a total of 60 Gy was delivered using 3-dimensional (3D) conformal radio-therapy. Patients received concomitant gemcitabine given intravenously at a dose of 175 mg/m2 weekly for 6 weeks, during the period of radiotherapy.
Results
Forty-two patients were enrolled with median age of 48 years (range 32-65) and Karnofsky performance status ranging from 60-90. At presentation only 16 patients (38%) had subtotal excision while the rest were just biopsied (62%). Twelve patients (28.5%) responded to treatment (2 patients achieved complete response and 10 patients experienced partial response). Additionally, 22 patients (52.4%) experienced stable disease for an overall disease control rate of 80%.
The treatment was well tolerated by most of the patients without any severe adverse reactions. We had 2 patients only (4.7%) with GIII toxicity (one patient developed anemia, and one experienced alopecia).
Median progression-free and overall survival was 7 and14 months respectively.
Conclusion
Concomitant chemoradiotherapy with gemcitabine is well tolerated and effective in treating newly diagnosed glioblastoma multiform and needs to be more investigated in a phase III multi-center trial after analysis of the MGMT promoter methylation of the tumors.

Introduction

Glioblastoma multiforme (GBM) is the most lethal form of primary brain tumors in adults. Maximal safe resection followed by radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ) is the current standard of care (1) (2). However, temozolomide is a relatively poor radiosensitizer, compared with other cytotoxic agents. (3), Also, Van Nifteric et al., 2007, confirmed that temozolomide itself is not a very potent radiosensitizer compared with gemcitabine. (4)

Gemcitabine (2', 2'-difluorodeoxycytidine) is a deoxycy--tidine analog antimetabolite acting as an excellent radio-sensitizer both in vitro and in vivo. (5)

The positive interaction between gemcitabine and radiotherapy is likely due to a combination of mechanisms that include deoxyadenosine triphosphate depletion, cell-cycle redistribution and inhibition of DNA synthesis and repair. (6)

In addition, short-term exposure to gemcitabine is sufficient to produce radio-sensitization when the drug is administrated 24–72 h before radiation, presumably due to the prolonged cellular effects mediated by extended retention of gemcitabine triphosphate [2', 2'-difluoro-2'-deoxycytidine phosphate (dFdCTP)]. (7)

Preclinical studies showed considerable uptake of gemcitabine in the brain (8). Additionally J. Sigmond et al., 2009 found that

in tumor samples, both gemcitabine and its metabolite diflurodeoxy uridine (dFdU) concentrations are high enough to enable radio-sensitization. (9)

In the present phase II study, we evaluated the activity and safety of gemcitabine (175 mg/m2/weekly) concurrently with radiotherapy in patients with newly diagnosed glioblastoma multiforme. The dose of gemcitabine adjusted based on the recommendation of a phase I study conducted by Fabi et al., 2008. (10)

Study Objectives

The primary end point was to assess the efficacy of Gemcitabine as a radio-sensitizer for newly diagnosed glioblastoma multiforme (GBM) in terms of response rate (RR) and progression-free survival (PFS) and also to assess treatment-related toxicity. The secondary end point was to assess over-all survival (OS).

Patients and Methods

Patients' criteria

Patients with newly diagnosed histologically proven supra-tentorial GBM (WHO grade IV) within 6 weeks from surgery (either biopsy or subtotal resection) were eligible for the study.

Age between 18 and 75 years, Karnofsky Performance Status (KPS) of 60 or more, life expectancy of >3 months, presence of evaluable and/or measurable disease after surgical procedure and adequate hematological, hepatic and renal functions were among inclusion criteria.

Major medical / psychiatric illness and history of previous malignancies within 3 years of diagnosis except for non-melanomatous skin cancer or carcinoma in-situ of the cervix or bladder rendered patients ineligible.

Treatment plan

Radiotherapy at a dose of 2.0 Gy per fraction given once daily, 5 days/week , over a period of 6 weeks, for a total of 60 Gy using Linear Accelerator of 6-15 dual energy was delivered using 3- dimensional (3D) conformal radiotherapy.

The radiotherapy volume includes the T2 or FLAIR abnormality plus a 2 cm margin. In patients with large lesions, after administering 46 Gy, irradiation will be continued on a boost volume limited to the contrast-enhancing mass in CT, or T1-MRI plus 2.5 cm margin. Twenty four hours up to 72 hours before the first day of radiotherapy, patients started concomitant gemcitabine given intravenously at a dose of 175mg/m2 (infusion duration =30 min) weekly for 6 weeks, during the period of radiotherapy. Antiemetic prophylaxis with dexamethasone 4 mg and metoclopramide 10 mg i.v. were given before each gemcitabine administration. All patients performed full lab, complete blood picture, liver functions and serum creatinine before starting the first dose of gemcitabine and repeated weekly.

Gemcitabine administration was discontinued for grade 3–4 neutropenia and/or thrombocytopenia, febrile neutropenia and grade 3–4 non-hematological toxicity except for nausea/ vomiting. At recovery, doses were permanently reduced to 75% of the target dose.

Full neurological assessment was done for every patient just to keep an eye over the course of the disease through-out the chemo-radiotherapy or during follow up. All patients were assessed with MRI-brain with contrast before starting the treatment, 4 weeks after the end of treatment coarse and every 12 weeks thereafter until evidence of disease progression. Magnetic Resonance Spectroscopy (MRS) was performed for follow up when available. In case of radiological confirmation of disease progression after the end of the adjuvant chemo-radiotherapy, we scheduled patients either for re-surgery (if feasible), followed by either ICE protocol (ifosfamide, carboplatin and etoposide.) or temozolomide if available. If not surgically fit we went directly for the salvage chemotherapy.

No patient received concomitant or adjuvant temozolomide as the trial was designed before the availability of temozolomide in our department.

Response and Toxicity assessment

We used the National Cancer Institute Common Terminology Criteria for Adverse Events V4 in toxicity assessment. (12) In terms of response to chemo-radiotherapy we used the McDonalds response criteria. (11)

Statistical analysis

Data were analyzed using the SPSS version 16; Qualitative variables were described as numbers and percentages. Chi-square or Fisher's exact test were used for comparison between groups; as appropriate. Quantitative variables were described as mean (±SD) and median. Independent t-test was used to compare mean of two different groups and one-way ANOVA was used to compare mean in three different groups.

Progression-free survival (PFS) and over-all survival (OS) were analyzed by Kaplan–Meier method including 95% CI.PFS was defined as the period of time elapsed from the first day of treatment to the date of disease progression, relapse or death. Overall survival was defined as the interval from the first day of treatment to the date of patient death or last follows up. "p value ?0.05" was considered to be statistically significant.

Qui-square test was used for the univariate and multivariate analysis.

Results

This study is a phase II trial, which included 42 patients with primary GBM (Glioblastoma Multiforme), presented to Clinical Oncology &Nuclear Medicine Department, Mansoura University Hospitals during the period from April 2008 till December 2010

Patients' criteria

Patients' characteristics are shown in table 1. Out of 42 patients, we had 25 (59.5%) male and 17 (40.5%) female. According to age stratification we had only 8 patients below 40 years (19%), 15 patients ranging from 41-50 years (35.7%) and 19 patients above 51 years (45.3%). Karnofsky scale was above 80 in 38% of patients.

Sixteen patients only (38%) underwent subtotal resection while 62% had just biopsy. Thirty one percent had tumors less than 5 cm. RPA classes IV, V, VI included 22 (52.4%), 15 (35.7%) and 5 (11.9%) patients respectively.

Safety

Treatment related toxicities are summarized in (Table 2). There were no instances of grade 3 or 4 neutropenia or thrombocytopenia. Only one patient developed grade 3 anemia and need just blood transfusion of 2 units of fresh blood without interruption of the pre-scheduled chemotherapy timing.

Table 1: patient characteristics

Patient characteristics	Number	Percent %
Sex		
Male	25	59.5
Female	17	40.5
Age (years)		
<40	8	19
41-50	15	35.7
>50	19	45.3
Karnofsky PS		
>80	16	38
60-70	26	62
Extent of surgery		
Sub-total resection	16	38
Biopsy	26	62
Tumor size		
2-5 cm	13	31
>5 cm	29	69
RPA classification		
IV	22	52.4
V	15	35.7
VI	5	11.9

Table 2: summary of treatment toxicities

	Grade I Patients No. (%)	Grade II Patients No. (%)	Grade III Patients No. (%)	Grade IV Patients No. (%)
Anemia	1 (2.4)	1 (2.4)	1 (2.4)	0
Neutropenia	3 (7.1)	2 (4.7)	0	0
Thrombocytopenia	3 (7.1)	0	0	0
Elevated liver enzymes	3 (7.1)	3 (7.1)	0	0
Nausea /Vomiting	30 (71)	5 (11.9)	0	0
Anorexia	10 (23.8)	6 (14.3)	0	0
Fatigue	20 (47)	3 (7.1)	0	0
Diarrhea	3 (7.1)	2 (4.7)	0	0
Alopecia	10 (23.8)	3 (7.1)	1 (2.4)	0
Otitis externa	1 (2.4)	0	0	0
Fever	3 (7.1)	0	0	0

Table 3: treatment response

Response	Patients No. (%)
CR	2 (4.7)
PR	10 (23.8)
SD	22 (52.4)
PD	8 (19)
Disease control rate (CR+PR+SD)	34 (80)
Tumor response rate (CR+ PR)	12 (28.5)

CR: complete response, PR: partial response,
SD: stationary disease, PD: progressive disease

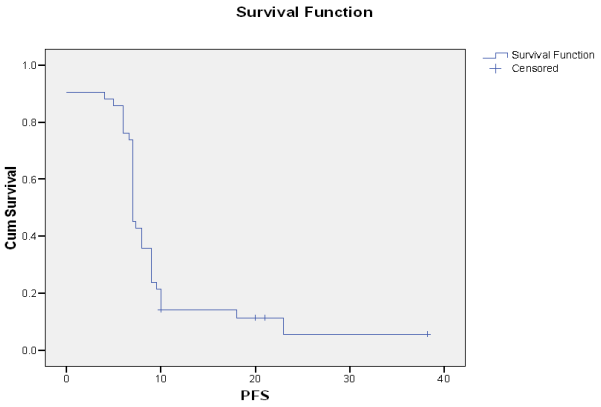

Figure 1. Progression Free Survival

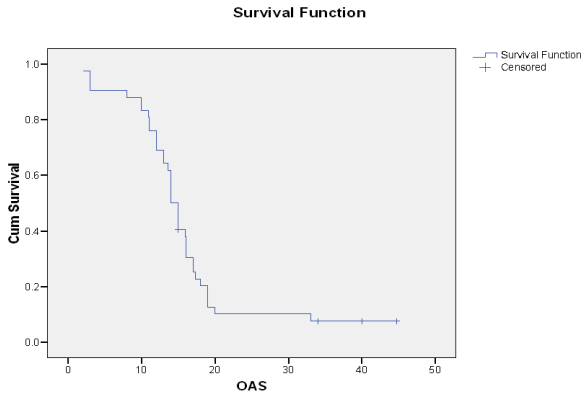

Figure 2. Overall Survival

Nausea and vomiting of G I, II in the first 3-5 radiotherapy sessions occurred in 35/42 patients and was controlled with corticosteroids and metoclopramide injections twice to 3 times daily, the rest of the patients were controlled only on metoclopramide injection. Grade I & II hypertransaminasemia were reported in six patients (14.3%), 3 of the 6 patients were under the treatment of the hepatotoxic drug phenytoin which was replaced with the safer antiepileptic valporoic acid. No treatment related grade IV non-hematological toxicities were reported; only one patient reported grade III radiation-induced alopecia.

Response and Survival

All patients completed the radio-chemotherapy treatment and were evaluable for response. Twelve patients responded to treatment (28.5 %), two patients (4%) had CR and 10 patients (23.8%) achieved partial response. 22 patients had stable disease (52.4%), resulting in an overall disease control rate of 80%. Eight patients (19%) developed progressive disease. (Table 3).All responding patients had undergone subtotal resection of the tumor. We have 3 patients who underwent re-surgery for a second time and one of them had a third surgery after 6 months.

Seven patients had received temozolomide after first progression, while 3 of them shifted to ICE protocol after progression on temozolomide. 20 patients received ICE protocol from 3-6 cycles according to response. The promising value in our study was the median PFS, which reached 7 months (95% CI= 6.66-7.34). The rate of patients who were free from progression at 6, 12 and 18 months was 76 %, 11.9% and 9.5 % respectively (Fig.1). While the median OS reached 14 months (95% CI 13.012-14.988) with OS at 6, 12,18 months was 90%, 69% and 19% respectively (Fig. 2).

This study has confirmed that the better the KPS the longer the PFS (p- 0.0001) and OAS (p- 0.002), as for the KPS <80 the PFS, OAS were (7,13 months) and for the KPS>80 they were (10,16 months) respectively.

The same significance were present when we correlate between age and PFS & OAS with p-values 0.001 & 0.003 respectively, as for age group below 40 years PFS and OAS were 20,33 months respectively and for 41-50 they were 9,15 months respectively and for patients above 51 years they were 7 and 13 months respectively.

The impact of extent of surgery was obvious during correlation between it and both PFS& OAS where patients who underwent near total excision had longer PFS and OAS (10& 19 months) than patients with just biopsy (7 & 13 months) with p-value 0.0001 & 0.0001 respectively.

Discussion

Along the past decade many trials used different radiosensitizers in treatment of newly diagnosed high-grade gliomas especially glioblastoma multiforme. (13) Concurrent use of radiation with a range of sensitizing agents, including various chemotherapeutic drugs, can augment treatment efficacy through several well-defined biologic pathways. Mechanisms of radiosensitization include spatial cooperation, cytotoxic enhancement, biologic cooperation, temporal modulation, and protection of normal tissues. (14) Temozolomide is the only chemotherapeutic agent that has been shown to provide a survival advantage when included with standard radiation therapy as an initial adjuvant approach for glioblastoma, an effect that has been associated with radiosensitization (15).

Though temozolomide is currently a first-line agent in the treatment of glioblastoma multiforme, unfavorable MGMT methylation status could help select patients appropriate for future therapeutic investigations (16).

In our study, Gemcitabine as a radio-sensitizer was quiet effective in newly diagnosed glioblastoma multiforme patients. First to declare is that we used gemcitabine in patients who cannot afford buying temozolomide, and governmental support coverage was not available. Temozolomide costs almost 14000 LE (1900 $) during the 6 weeks in a dose of 75 mg/m2 daily during radio-therapy, while gemcitabine costs only 2400 LE (320 $) through entire radiotherapy course at dose of 175 mg/m2 weekly for 6 weeks. Second to declare is that the OS in this study can't be referred to gemcitabine, as after progression, management was individualized by either giving the patients chance of temozolomide if available, and if not we had to give them ICE protocol (ifosfamide 2gm/m2 D1-3, etoposide 100mg/m2 D1-3, and carboplatin AUC 5 in D1 only) /3 weeks for 3 cycles then to assess the condition for either stoppage or continuation if there is quite response. Re-surgery was also an option after progression.

The first study to demonstrate that gemcitabine passes through the blood–tumor barrier in GBM patients was performed by Sigmond et al., 2009. They proved that, both plasma and tumor levels of Gemcitabine and its metabolite diflurodeoxy uridine (dFdU) are high enough to enable radiosensitization. Clinical studies using gemcitabine in combination with radiation were therefore warranted, especially in patients who are not expected to benefit from radiation with temozolomide. (9)

The observed activity of gemcitabine concomitant with radiotherapy at a dose of 175 mg/ m2/w in a phase I study performed by Fabi et al., 2008, had been considered interesting enough to support a phase II study of concurrent gemcitabine-radiotherapy as first line treatment in GBM.

Gemcitabine was also investigated, as a radiosensitizer, in a phase I clinical trial performed by Maraveyas et al., 2005 for treatment of cases with brain metastasis with a promising response rate of 54.5%. Based on these encouraging data, we decided to open a phase II trial in our institution to clarify the role of this drug in newly diagnosed GBM patients. (17) During our study processing, Metro et al., 2010 published the results of their early similar trial of concurrent gemcitabine and radiotherapy plus adjuvant temozolomide. (18)

The promising value in our study was the PFS, which reached 7 months (95% CI 6.66-7.34). The rate of patients who were free from progression at 6, 12 and 18 months was 76%, 11.9% and 9.5 % respectively. Similarly, Mero et al., 2010 in their similar trial of fixed dose rate of gemcitabine as a radiosensitizer in GBM reported PFS of 6.8 months. (18)

These results compare favorably with the corresponding values of 6.9 months and 14.6 months for PFS and OS respectively obtained with temozolomide concomitantly with radiotherapy (1) considering the fact that all patients in our study had residual disease after surgery and just biopsy was performed for most of them (62%).
Indeed it is difficult to compare our results with those achieved in similar trials of concomitant radiotherapy - temozolomide with or without adjuvant temozolomide where 17.5-34.5% of their patients had performed complete tumor resection. (11) (19) (29)

In the present study, the promising values of response rate and PFS purely reflect the role of Gemcitabine as a radio-sensitizer; nevertheless, OS was secondary objective and is more likely has been influenced by successive therapies administered at disease progression. Regarding the safety of the Gemcitabine-Radiotherapy combination, it was well tolerated by the study group, as there were no grade 4 toxicities and only one patient experienced grade 3 radiotherapy-related alopecia and another patient suffered from grade 3 anemia and needed blood transfusion.

Our results confirmed that better surgical intervention; younger age and better performance status were associated with better results in sub-group analyses. Similar results were proved by other investigators. (20)(13)

The treatment-related morbidity was better than that observed with topotecan (21) or paclitaxel. (22) given concurrently with

radiotherapy and gemcitabine appeared to perform better in terms of hematological toxicity, where no suspension of gemcitabine was required compared to that of both drugs discontinuation for grade 3, 4 neutropenia.

All other new agents in the post-temozolomide era are added to temozolomide during radiotherapy with more stratification of the patients as regard cellular methylation (MGMT), e.g. Nimotuzumab, where there is higher cost and more toxicity profiles. Survival was better for the methylated subgroup (23.4 months) as compared with the non-methylated one (19 months). (23) (28)

Stupp et al., 2014, investigated Cilengitide in a large randomized trial. All treated patients had methylated MGMT and the OAS was 26.3 months in both Cilengitide and control groups. (24) Therefore, we can use gemcitabine in patients for whom little or no benefit is expected from agents such as temozolomide which would be the case of individuals with unmethylated MGMT promoter (25) (26) (27). This is supported by the data published by metro et al., 2010 who concluded that the radiosensitizing effect of gemcitabine can be achieved irrespective of the methylation status of the MGMT promoter. In fact, our small number of study population and the lack of information about the methylation status necessitate us to recruit more patients with further stress on the methylation status of the patients in the near future.

In conclusion, our study showed that the use of gemcitabine given concurrently with radiotherapy is clinically active as a radiosensitizer for newly diagnosed GBM and might be worthy of being investigated further in future studies of chemo-radiotherapy after analysis of the MGMT promoter methylation of the tumors.

Disclaimer

There were no conflict of interest with Eli-Lilly as a provider of Gemzar to Mansoura University Hospitals. All patients received the treatment after approval of our institutional reviewer board and after their informed consent from the patient him/herself or her relatives as they were aware by the investigational nature of the treatment**.**

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