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ORIGINAL ARTICLE

Combination of Cisplatin and Temozolomide versus Carboplatin and Etoposide in the Treatment of Recurrent High Grade Glioma Patients

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ABSTRACT

Background: Recurrent high-grade glioma patients exhibited poor survival. Chemotherapy such as cisplatin and Etoposide may overcome tumor cell resistance. Multiple phases I and II trials have revealed the safety and efficacy of Temozolomide (TMZ) combined with interferon, nitrosoureas, bevacizumab and other chemotherapeutic agents such as irinotecan, pegylated doxorubicin and cisplatin given in progressive as well as recurrent glioblastoma multiforme (GBM). We aimed to evaluate the impact of cisplatin plus TMZ versus Carboplatin plus Etoposide in treating recurrent high-grade glioma on clinical outcomes.

Methods: 40 patients were enrolled in this study, where 25 patients diagnosed with recurrent high-grade glioma received cisplatin plus TMZ versus, the other 15 patients received Carboplatin and Etoposide to evaluate toxicity and survival in both groups.

Results: Both studied arms have shown tolerable toxicity findings with no statistical difference. Progression was observed more in patients who received Carboplatin + Etoposide protocol than cisplatin + TMZ. However, of no statistical significance (P = 0.44), the median PFS of both arms were 5 ± 0.63 and 7 ± 1.87 months, median OS was 9 ± 1.54, and 11 ± 1.66 months, respectively, without any significant difference.

Conclusions: Cisplatin plus TMZ combination had shown an accepted toxicity profile and survival outcome in terms of PFS and OS compared to Carboplatin plus Etoposide protocol without significance. MGMT, EGFR, and PI3K molecular studies could promise survival gains.

Keywords: Cisplatin; Temozolomide; Carboplatin; Etoposide; Glioma.

INTRODUCTION

Primary CNS tumor incidences were 5.34%, 7.25% and 4.49% in upper, middle and lower Egypt, respectively. The incidence rate was 6.9 and 5.8 for males and females, respectively, with 9.0 in 100.000 as an age-standardized incidence rate in males, while 8.0 in 100.000 in females [1]. Recurrent GBM patients exhibited poor prognosis with half year time as average survival [2].

Neurosurgery prior to local radiotherapy 60Gy/200cGy/30fr with concurrent 75 mg/m^2 daily Temozolomide then 150-200mg/m^2 proposed as an adjuvant for six cycles as 28 days cycle, considered as the standard mainstay treatment for high-grade glioma patients with around expected 14.6 months median overall survival [3]. Enzyme O6-methylguanine-DNA- methyltransferase could repair damage and epigenetic silencing of deoxyribose nucleic acid resulting from Temozolomide and other alkylating chemotherapy. This enzyme is

considerable for TMZ response prediction and effectiveness [4,5].

Limitations of chemotherapy proposal in primary and recurrent glioblastoma emphasized by acquired and drug innate cells' resistance, so in need of understanding improvement of resistance mechanisms and action of platinum agents with TMZ [6]. The rationale for cisplatin combinations with TMZ was because of the synergistic effect of cisplatin via decreased MGMT activity, increasing TMZ activity rather than TMZ as a single agent with tolerable toxicity profiles reported in many studies [7].

Carboplatin is an alkylating agent of great value in different solid tumors treatment. It is characterized by a robust dose-response relationship in vitro malignant glioma cells and of great cytotoxic potentiality against human gliomas in vitro [8,9]. Etoposide is one of the semisynthetic podophyllotoxin antagonizing topoisomerase II, which results in activity demonstration against gliomas and other brain tumors [10]. Carboplatin and Etoposide could cross the blood-brain barrier [11,12] and were detected in cerebrospinal fluid. Retrospective analysis suggests that treatment with pulsed reduced rate radiotherapy in addition to bevacizumab may significantly prolong PFS and overall survival compared with bevacizumab alone for recurrent high-grade glioma [13].

Multiple trials of phases I and II have revealed the safety and efficacy of TMZ combined with interferon, nitrosoureas, and bevacizumab and some other chemotherapeutic agents such as irinotecan, pegylated doxorubicin, and cisplatin given in progressive as well as recurrent GBM. [2,14,15,16].

METHODS

A prospective cohort study, were conducted at clinical and medical oncology departments in tertiary referral hospitals between the period December 2018 to the end of 2021 and the data were collected from archived patients' files or direct contact with them. Written informed consent was obtained from all participants and the study was approved by the ethical research committee of the Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans (Approval no:9563).

Inclusion criteria: Confirmed histopathological evidence of GBM, accepted complete blood count; platelets count more than 100.000/ mm^{-3}, neutrophils more than 1500 mm^{-3}. Accepted liver and kidney functions, bilirubin and creatinine levels less and equal to 1.25 times of standard limit, Karnofsky more and equal to 60, patients received radiotherapy in 60 Gy/ 200 cGy / 30 fractions with concurrent and adjuvant Temozolomide and not accessible for re-surgery or re-irradiation.

Exclusion criteria; Data shortage and treatment omission due to uncontrolled toxicity according to National Cancer Institute-common toxicity criteria. [17].

O the 40 patients included in this study, 25 patients were enrolled in the arm who received cisplatin plus Temozolomide; on the first day of the cycle, 40 mg cisplatin was dissolved in 0.9 %, 500 cc saline intravenously over one-hour duration before the start of Temozolomide dose, 30 mg cisplatin was proposed on day 2-3 before the second and third dose of Temozolomide, 50 mg/ m^2 Temozolomide was proposed daily, continuously until unaccepted toxicity or proved progression, the cycle was as 28 days. All patients underwent good hydration and antiemetic administration. In controlled toxicities, the dose of Temozolomide was decreased by 25%.

Fifteen patients were enrolled in the arm who were proposed Carboplatin plus Etoposide; An intravenous Carboplatin infusion dose of 100 mg/m^2 was proposed 30 minutes before Etoposide administration over one hour and Etoposide 120 mg/ m^2 was received intravenously for three days, the cycle was as four weeks for 12 cycles.

Patients were evaluated by clinical and radiological assessments, magnetic resonance image (figure 1), computed tomography with contrast and others such as plain chest x-ray, pelvic and abdominal ultrasound. Toxicity and survival analysis were evaluated for both groups.

Statistical analysis

Continuous variables were expressed as the mean ± SD & median (range), and the categorical variables were expressed as a number (percentage). The percentage of categorical variables was compared using Pearson's Chi-square test or Fisher's exact test when was appropriate. The trend of change in the distribution of relative frequencies between ordinal data was compared using the Chi-square test for trend. Overall Survival (OS) was calculated as the time from diagnosis to death or the most recent follow-up contact (censored). Progression free survival (PFS) was calculated as the most recent follow-up contact that patient was known as progression-free. All tests were two-sided. A p-value

<0.05 was considered significant. All statistics were performed using SPSS 16.0 for windows (IBM Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Twenty-six patients out of 40 were > 50 years old, 28 out of 40 were males, 21 out of 40 were on the 80 karnofsky scale, and 37 out of 40 underwent subtotal surgery or biopsy. There was no statistical difference between patients who received cisplatin + Temozolomide and those who received Carboplatin + Etoposide (Table 1).

Toxicity profile

Both studied arms showed tolerable toxicity findings with no statistical difference regarding hematological toxicity, vomiting, fatigue, somnolence , thrombo -embolic problems, hypotension and ototoxicity (table 2).

Survival assessment

Progression was observed more in patients who received Carboplatin + Etoposide protocol than those who received cisplatin + Temozolomide. However, of no statistical significance, p = 0.44, median PFS in months of both arms were 5 ± 0.63, 7 ± 1.87, respectively, with a p-value = 0.16 of no significance.

Overall survival in patients who received cisplatin + Temozolomide was better than in those who received Carboplatin + Etoposide; median OS in months was 11 ± 1.66, 9 ± 1.54, respectively of no statistical significance p value = 0.1 (Table 3, figure 1).

Table 1: Characteristics of both studied arms.

Items	Total	Cisplatin + temozolamide	Carboplatin + etoposide	P value
Age				
≤ 50	14 (35%)	8 (32%)	6 (40%)	0.73
> 50	26 (65%)	17 (68%)	9 (60%)	
Sex				
Male	28	15 (60%)	13 (86.7%)	0.15
Female	12	10 (40%)	2 (13.3%)	
KPS				
60	2 (5%)	1 (4%)	1 (6.7%)	0.93
70	3 (7.5%)	2 (8%)	1 (6.7%)	
80	21 (52.5%)	14 (56%)	7 (46.7%)	
90	14 (35%)	8 (32%)	6 (40%)	
History of initial surgery				
Gross total resection	3 (7.5%)	3 (12%)	0 (0%)	0.27
Subtotal resection or biopsy	37 (92.5%)	22 (88%)	15 (100%)	

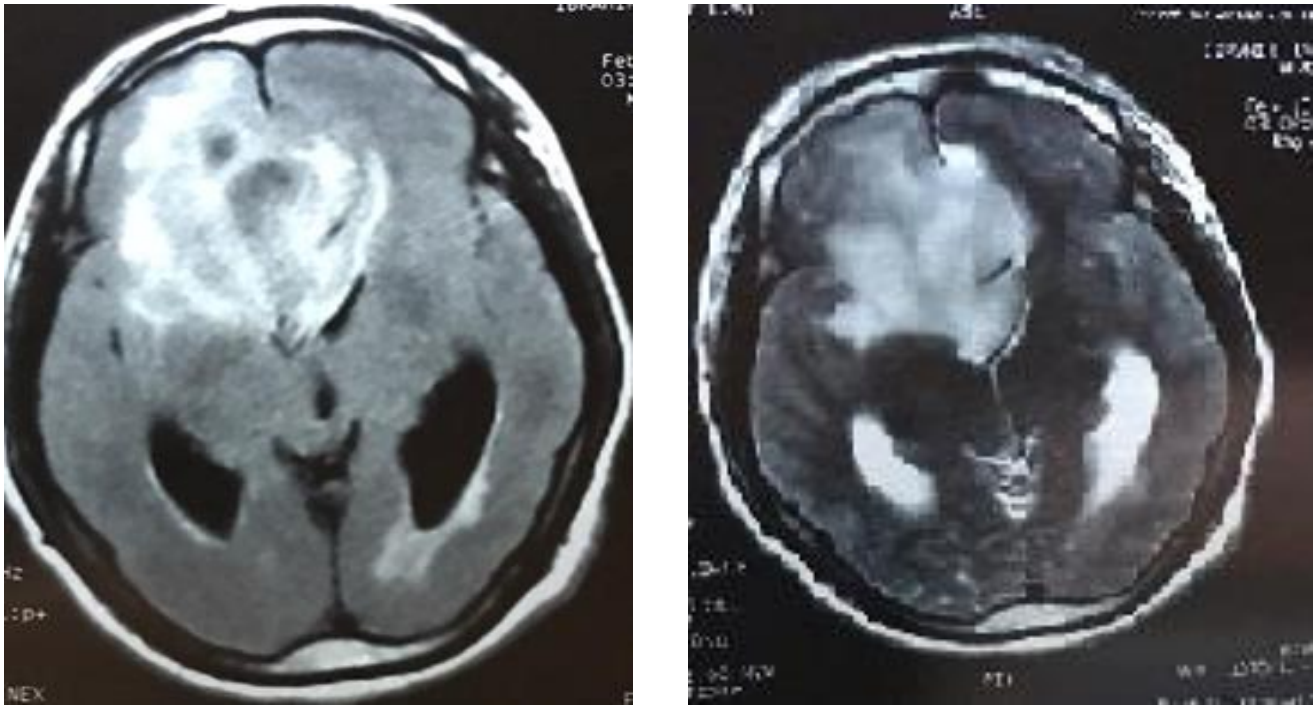
Table 2: Toxicity profile of both arms.

Items	Total	Cisplatin + temozolamide	Carboplatin + etoposide	P value
Leucopenia				
G1,2	16 (40%)	8 (32%)	8 (53.4%)	0.21
G3	4 (10%)	2 (8%)	2 (13.3%)	
G4	4 (10%)	2 (8%)	2 (13.3%)	
No	40 (40%)	13 (52%)	3 (20 %)	
Anemia				
G1,2	21 (52.5%)	12 (48%)	9 (60%)	0.57
G3	4 (10%)	2 (8%)	2 (13.3%)	
G4	2 (5%)	1 (4%)	1 (6.7%)	
NO	13 (32.5%)	10 (40%)	3 (20%)	
Thrombocytopenia				
G1,2	8 (20%)	7 (28%)	1 (6.7%)	0.15

Items	Total	Cisplatin + temozolamide	Carboplatin + etoposide	P value
G3 No	1 (2.5%%) 31 (77.5%)	1 (4%) 17 (68%)	0 (0%) 14 (93.3%)	
Vomiting G1,2 G3 G4 No	 20 (50%) 1 (2.5%) 1 (2.5%) 18 (45%)	 14 (56%) 1 (4%) 1 (4%) 9 (36%)	 6 (40%) 0 (0%) 0 (0%) 9 (60%)	0.50
Fatigue G1,2 G3 G4 NO	 14 (35%) 4 (10%) 2 (5%) 20 (50%)	 10 (40%) 2 (8%) 2 (8%) 11 (44%)	 4 (26.7%) 2 (13.3%) 0 (0%) 9 (60%)	0.55
Somnolence G1,2 G3 G4 N0	 9 (22.5%) 5 (12.5%) 2 (5%) 24 (60%)	 4 (16%) 2 (8%) 2 (8%) 17 (68%)	 5 (33.3%) 3 (20%) 0 (0%) 7 (46.7%)	0.39
Thromboembolic G1,2 G3 G4 NO	 8 (20%) 4 (10%) 2 (5%) 26 (65%)	 5 (20%) 2 (8%) 1 (4%) 17 (68%)	 3 (20%) 2 (13.3%) 1 (6.7%) 9 (60%)	0.94
Hypotension G1,2 No	 1 (2.5%) 39 (97.5%)	 0 (0%) 25 (100%)	 1 (6.7%) 14 (93.3%)	0.37
Ototoxicity G1,2 No	 7 (17.5%) 33 (82.5%)	 6 (24%) 19 (76%)	 1 (6.7%) 14 (93.3%)	0.22

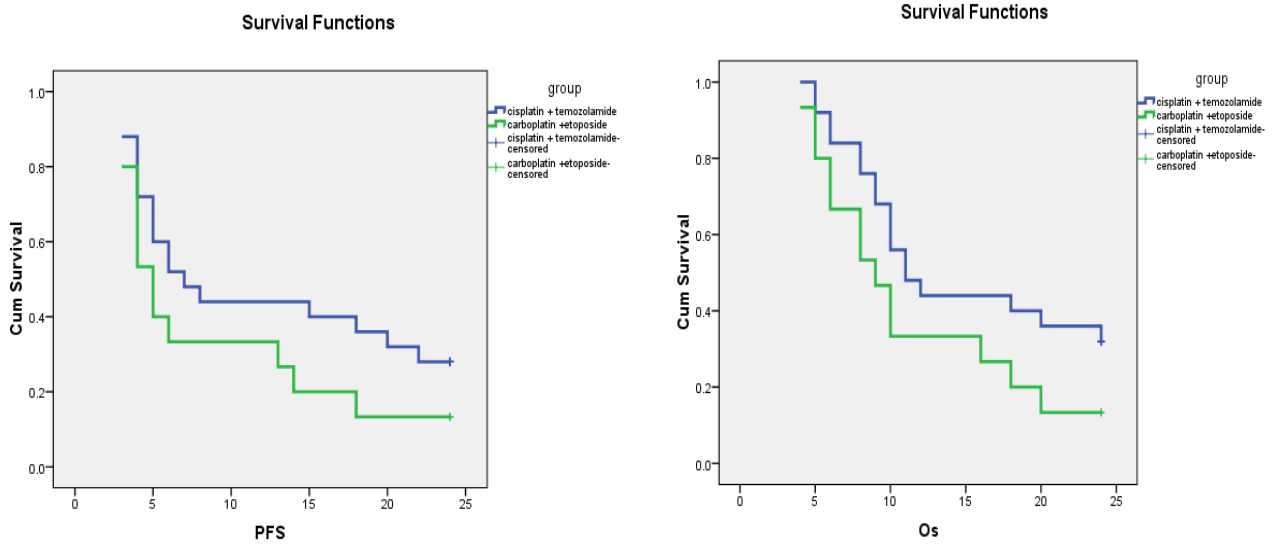
Table 3: survival outcome.

Item	Total	Cisplatin + temozolamide	Carboplatin + etoposide	P value
Progression Absent Present	 9 (22.5%) 31 (77.5%)	 7 (28%) 18 (72%)	 2 (13.3%) 13 (86.7%)	0.44
PFS Median (month) Range	 6 ± 0.78 4.45 – 7.54	 7 ± 1.87 3.32 – 10.67	 5 ± 0.63 3.7 – 6.24	0.16
Death Absent Present	 10 (25%) 30 (75%)	 8 (32%) 17 (68%)	 2 (13.3%) 13 (86.7%)	0.26
OS Median (month) Range	 10 ± 0.9 8.23 – 11.76	 11 ± 1.66 7.73 – 14.26	 9 ± 1.54 5.97 – 12	0.1



(A) (B)

Figure 1: MRI with contrast shows large intra axial frontal lobe GBM recurrent lesion involved the genu, body of corpus callosum with obstructive changes.



(A) (B)

Figure 2: Kaplan Meier plot shown PFS and OS of the studied patients, cisplatin + temozolomide versus carboplatin + etoposide.

DISCUSSION

In this prospective cohort study, patient's characteristics of recurrent GBM were observed and the toxicity and survival outcome of patients who proposed cisplatin + Temozolomide versus Carboplatin + Etoposide protocols were studied.

In our study, the major toxicities of patients who were proposed cisplatin plus Temozolomide were as a hematological manifestation in the form of 12(48%) patients were G1,2, 2(8%) patients were G3,1(4%) was G4 anemia.14(56%) patients showed G1,2, 1(4%) patient was G3 and 1(4%) was G4 vomiting. Fatigue was manifested in 10(40%)

patients as G1,2, 2(8%) patients as G3 and G4 for each. This nearly agrees with the toxicity profile studied by [6] in 27 patients who received cisplatin plus Temozolomide, who exhibited 10(37%) G1,2, 2 (7%) G3, and 1(4%) G4 anemia. 10(37%) patients manifested G1,2, 1(4%) G3,1 (4%) G4 nausea and vomiting while fatigue was observed in 8(30%) patients as G1,2, 2(7%) patients as G3.

In the present study, it was wished for better survival outcomes and overcoming chemoresistance. In the cisplatin plus Temozolomide arm, the median PFS was 7 ± 1.87 with a range of 3.32 – 10.67 (months), and the median OS was 11 ± 1.66 with a range of 7.73 – 14.26 (months). In Carboplatin plus Etoposide, the median PFS was 5 ± 0.63 with a range of 3.7 – 6.24, and the median OS was 9 ± 1.54 with a range of 5.97 – 12 (months).[6] reported that the median TTP was 23 ± 3.4 with a range of 16.2 – 29.7 (weeks), and the median OS was 50 ± 9.5 with a range of 31.3 – 68.6 (weeks). This nearly agrees with our objectives and results as well as the study was conducted by [18] who comprised 37 patients diagnosed with progressed or recurrent glioblastoma, received Temozolomide 50 mg / m^2 without interruption up to progression or uncontrolled toxicity, the patients underwent MGMT methylation study, 18(49%) out of 37 patients were received bevacizumab previously and concluded that the median PFS was two months,95% CI range of 1-4, the median OS was seven months,95% CI range 5-12 and survivors median follow up was 19 month, provided safety toxicity profile and activity of such daily protocol, bevacizumab naïve patients or who had shown bevacizumab failure had a favorable six month PFS and their median OS was 13 month, recommended PI3K complex mutation study as this may convey a better prognosis. Another study stated that 25 patients were proposed a combination of bevacizumab, Carboplatin and irinotecan had shown favorable survival results as the median OS with 7.99 months as a median follow-up for all patients, median PFS was 2.3 months at 95% CI ranged 1.8 – 3.6 months and median OS was 5.8 with 95% CI range of 4 – 7 months [19], this was different to our results because of different patient[s'] characteristics in previously treatment combinations.

Silvani et al. studied the combination of cisplatin in the first and second days of 4 weeks cycles, 40 mg/m^2 intravenously and 200 mg / m^2 Temozolomide on day 2 to the six[th] day orally. The median TTP was 33 weeks [20]. Another dosage of 75 mg/ m^2 cisplatin was given on day 1in combination with 2 to 6 days of 130 mg/m^2 Temozolomide with a reported 18.4 weeks median PFS at 95% CI, ranging 13 to 25.9 weeks, median OS was 48 weeks, 95%CI range was 41.6 to 60 weeks with tolerable and safe toxicity, the majority was as hematological and gastrointestinal and ototoxicity [21]. Previous findings were similar to the present study. David Bergman et al. stated that the overall median survival was 6.6 months (7.2 months with Fractionated stereotactic radiosurgery vs. 4.8 months with chemotherapy alone in the form of irinotecan, Etoposide, temozolomide combinations, P = .11)[22], Beatrice Detti et al., reported that no significant survival difference was found between the use of bevacizumab alone and in combinations with other chemotherapy agents: Median OS was 9.4 months (7.7–13.4) and 8.9 months (95% CI 7.2–11.7), respectively; median PFS was 6.9 months [23], the difference may be due to variance of clinicopathological features and sample size of the studied patients.

Franceschi et al. studied Carboplatin and Etoposide combinations in 30 patients. They revealed that the median PFS was four months at 95%CI ranging from 3 to 5 months, and the median OS was ten months,95%CI range 5 to 13 months. G3 or four neutropenia in 6(20%) patients and ototoxicity in1(3.3%) patients were reported [24]. Survival outcomes agree with our results. While there is a difference in toxicity, as we did not observe G3 or four ototoxicity, this may be due to different patient[s'] tolerability and co-morbidities.

In the current prospective study, toxicity and survival were analyzed for both groups, and this strength of our study, although of small sample size and the absence of molecular study of MGMT methylation, EGFR, and PI3K complex mutation, we recommend further extensive studies with the feasibility of previous molecular analysis to stratify patients and overcoming chemoresistance in favor of better clinical gains.

Conclusions

Cisplatin plus Temozolomide combination had shown an accepted toxicity profile and survival outcome in terms of PFS and OS compared to Carboplatin plus Etoposide protocol without significance. MGMT, EGFR, and PI3K molecular studies could promise survival gains.

Conflict of interest: None

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