# Cisplatin and Vincristine in High Grade Glioma before Radiotherapy: A Phase II Trial

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**Abstract: Aim:** The aim of this phase II study is to evaluate response rate, time to progression, and toxicity of preirradiation chemotherapy with cisplatin / vincristine followed by radiotherapy in patients with high grade gliomas. **Material and methods:** All patients must have a histologic confirmation of high grade gliomas according to the World Health Organization (WHO), no prior chemotherapy or radiotherapy for their brain tumor. A total of four to eight weakly cycles of cisplatin (25mg/m$^2$) and vincristine 1.4 mg/m$^2$ were given. Radiation therapy was given after that to a total dose of 60 Gy in 2 Gy/fraction over 6 weeks. **Results:** Thirty five patients were enrolled in this study. No complete response was obtained. PR was seen in 10/34 patients. Stabilization of disease was obtained in 20/34 patients. Median time to progression after radiotherapy was 6.9 months for stable and responding patients. 7/34 of patients were considered as long-term survivors (>18 months; range: 19-36 months). Mean survival duration was 14.1 months for the whole group. Median survival rates at 6 and 12 months were 85% and 38%, respectively. Toxicity was not high and mainly hematological due to the chemotherapy given. **Conclusion:** Preirradiation chemotherapy may offer some theoretical advantages, especially with regard to discovering more active agents, but its real value and possible advantages still have to be determined.

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**Key words:** Cisplatin, Vincristine, Before Radiotherapy, Glioma

## 1.Introduction

Primary malignant brain tumors has very poor prognosis. Surgery and radiotherapy are now the standard therapies for treatment of anaplastic astrocytoma (grade III) and glioblastoma multiforme (grade IV). In spite of very active fundamental research on these tumors, there is no effective treatment available. (1)

The overall prognosis of glioblastomas remains unfavorable in spite of the major advances that have been made in therapeutic methods such as surgery, radiotherapy, chemotherapy and various combinations and the median survival time ranges from 6 to 12 months. Few patients are still alive after 2 year of diagnosis.(2)

Surgical resection is considered to be the initial therapeutic approach. However, due to the infiltration of malignant cell into the surrounding brain tissue and its migration in the brain it is rarely curative. Resection represents a strong prognostic factor since there is a good correlation between maximum tumor resection and patient survival. However, because of the volume or the site of the tumor at an important brain site total resection is frequently impossible. (3)

Postoperative radiotherapy only produces a minor prolongation in survival with median survival, increasing from 4.5-6 months in the case of surgery only to 9-10 months for a combination of surgery and postoperative radiotherapy.(4)

Chemotherapy has a limited impact on survival, despite the meta analysis of randomized cases that suggested a survival increase of 5 to 10% at two years by the use of adjuvant chemotherapy for high grade astrocytoma. The median survival has increased from 9.4 to 12 months. The most commonly used chemotherapy consisted of nitrosoureas such as Carmustine. (5)

The timing of chemotherapy and radiotherapy is the subject of much debate. Preirradiation or neoadjuvant chemotherapy has several potential advantages. First, neoadjuvant chemotherapy allows for the early treatment of infiltrating malignant cells that may be at or beyond the borders of radiation field. Second, drug delivery to the tumor cell is maximized due to the absence of radiation induced vascular permeability changes. Further, true assessment of the efficacy of chemotherapy can be easily done if it is given before radiotherapy. However, some patients require early radiotherapy due to their chemoresistant tumor cells.(6)

The primary objectives of this phase II study were to evaluate response rate, time to progression, and toxicity of preirradiation chemotherapy with cisplatin / vincristine followed by radiotherapy in patients with anaplastic astrocytoma, glioblastoma multiforme and oligoastrocytoma.

## 2. Patient and methods

### Eligibility criteria

All patients must have had histologic confirmation of diffuse infiltrating anaplastic astrocytoma, glioblastoma multiforme or oligoastrocytoma according to the World Health Organization (WHO) criteria in order to participate in

this trial (7). All patients had no prior chemotherapy or radiotherapy for their brain tumor. Exclusion criteria included patients with age less than 18 years, multifocal brain tumors, creatinine more than 0.2 mg/dl above the upper limit of the normal level, elevated direct billirubin, aspirate amine transferase (AST) > two times normal, uncontrolled infection, coexistent malignant disease or major medical problems, Eastern Cooperative Oncology Group (ECOG) performance score of 4 and pregnancy or lactation. All patients provided written informed consent before study enrollment. The pathology and grade of tumor were determined at the Department of Pathology in Zagazig University Hospital.

**Chemotherapy:**

All patients were hospitalized at the Clinical Oncology Department in Zagazig University Hospital to administrate the chemotherapy after surgery in the neurosurgery department in the same university. Hydration, which consisted of 2 liters of 0.9% NaCl, was given before starting each cycle of chemotherapy. A total of four to eight weakly cycles of cisplatin (25mg/$m^2$) and vincristine (1.4 mg/$m^2$, max 2 mg) were given. If the total WBC count was less than 3000/ml or platelet count was less than 100,000 or Hgb was less than 9 g/dl then delays for administration of chemotherapy were allowed and treatment was postponed for 1 weak. Chemotherapy was discontinued and radiotherapy initiated if a patient had a greater than 25% increase in contrast enhanced tumor volume or poorer neurological status on a stable dose of corticosteroids.

Antiemetic treatment (intravenous ondanestron 8 mg) was systematically administered. Methylprednisolone or Dexamethasone was not used as anti-emetics due to their effects on the blood brain barrier. Their dose used to control brain edema were kept as constant as possible to ensure that changes in magnetic resonance imaging (MRI) scans used to determine tumor response or progression was not related to changes in glucocorticoid doses.

**Radiation therapy**

Radiation therapy was administered at the Clinical Oncology Department in Zagazig University Hospitals after the eighth week with the routine dose and schedule that are usually used for glioblastomas patients. The initial target volume included the preoperative volume of enhancement on computed tomography (CT) or magnetic resonance imaging (MRI) and the surrounding area of brain edema with a 2 cm margin. This volume received 45 Gy (2Gy / fraction to isocenter) given on consecutive weekdays for 4.5 weeks. This volume was then reduced to include the contrast-enhancing tumor volume only. The total radiation dose to this region was 60 Gy in 2 Gy/fraction over 6 weeks. All patients were to have isodose plots generated on a minimum of three contours for the initial volume, one at central axis, one superior to the central axis (2 cm below the superior field edge), and one inferior to the central axis (2 cm above the inferior field edge). A single central axis isodose curve was required for the boost volume. For the purposes of quality control, a minor deviation was defined as having occurred if the 100% isodose envelope missed part of the target volume but the 90–95% isodose envelope enclosed the target volume, and a major deviation if only the <90% isodose envelope (but not the 100% isodose envelope) enclosed all of the target volume.

**Patient evaluation**

Each patient had a baseline evaluation formed of history, general physical examination, neurological examination, complete blood count, serum chemistry (billirubin, AST and creatinine) and head CT or MRI scan with contrast within one week of initial therapy. Complete blood picture and serum chemistry were repeated weekly during chemotherapy. Following completion of chemotherapy treatment, baseline evaluations were repeated then they were repeated again after finishing the radiotherapy course and then every 3 months for 1 year, then every 6 months for the next 2 years.

**Assessment of toxicity and response**

National Cancer Institute common toxicity criteria were used throughout. The chemotherapy was delayed when WBC count was 3000/ml or less or platelets 100,000/ml or less at the beginning of each cycle, until marrow recovery. Radiation therapy was delayed until marrow recovery if WBC count 2000/ml or platelet count 50,000/ml, until marrow recovery. Cisplatin dose was decreased 50% when serum creatinine was between 0.8 to 1.2 mg/dl above the upper limit of normal and treatment was discontinued when serum creatinine was greater than 1.2 mg/dl above the upper limit of normal, or if grade 3 or higher neurotoxicity or ototoxicity occurred.

We determined the response to chemotherapy and radiotherapy by comparing the neurological examinations and the contrast enhanced MRI imaging performed before starting the chemotherapy with the ones done 1 month after ending the radiotherapy and every three months after that. We used the following response criteria defined by Mac Donald to evaluate the response of treatment (8). Tumor size was defined as the product of the two largest perpendicular tumor diameters. CT or MRI scans were done before and after the biopsy or surgery then every 4 cycles of chemotherapy, 1 month after the end of radiotherapy or when a new neurological event happened. A complete response (CR) was defined as the complete disappearance of all contrast-enhancing tumors in a patient with a stable or improving neurological

examination. A partial response (PR) was defined as a >50% reduction in the contrast-enhancing tumor size with a stable or improving neurological examination. Progressive disease (PD) required a greater than 25% increase in the size of the contrast-enhancing tumor or progressive neurological abnormalities. Stable disease (SD) was defined as those patients whose clinical status and CT or MRI sizes did not meet the criteria for CR, PR or PD. If a patient completed therapy without progression, follow-up was at intervals of 3 months for 1 year, then every 6 months for the next 2 years. Time to progression was defined as the time from start of therapy to the first sign of disease progression. Survival was measured from the date of diagnosis. Overall survival and disease free survival was estimated using Kaplan Meier method.

## 3. Results

### Patient characteristics:

Between March 2009 and December 2011, 35 patients were enrolled in this protocol (24 men and 11 women). Patient characteristics are described in Table I. Median age was 56 years (range 38 to 68 years). Thirty-two tumors were classified as grade IV with atypical cells in 100% of the tumors, necrosis in 94% mitosis in 91%, and proliferation of the capillary endothelium in 86% of cases. Three tumors were classified as grade III because both necrosis and endothelial proliferation were absent. Twenty one patients underwent maximum debulking while fourteen patients underwent a biopsy alone according to the comparison between the preoperative and post operative imaging studies. Antiepileptic drugs and corticosteroids were given to all patients. All patients had a measurable tumor and were assessed in terms of treatment toxicity, tumor response and survival.

**Table 1: patient characteristics (n=35)**

| | |
|---|---|
| *Age: median 56 years (range 38 to 73 years)* | |
| **Sex** | |
| Male | 24 |
| Female | 11 |
| **Histology** | |
| WHO grade III | 3 |
| WHO grade IV | 32 |
| **Initial surgery** | |
| Biopsy alone | 14 |
| Debulking | 21 |

### Treatment:

Thirty patients (86%) completed all 8 scheduled chemotherapy cycles. One patient received 2 cycles only, 2 patients received 4 cycles only and 2 received 6 cycles only. Of these 5 patients, 4 discontinued chemotherapy treatment due to clinical progression of the disease while receiving chemotherapy and 1 died as a result of an intercurrent disease. All 34 patients were given the full scheduled dose of radiotherapy.

### Response

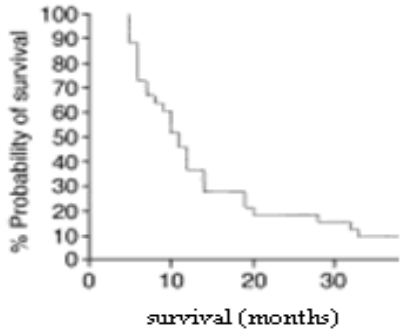
All patients had measurable disease on MRI scans. Tumor sizes before and after chemotherapy were calculated on the two greater axis products for all patients.

No complete response was obtained. PR was seen in 10/34 patients (29.4%). Stabilization was obtained for 20/34 patients (58.8%). Median time to progression after radiotherapy was 6.9 months for stable and responding patients. 4 patients (11.8 %) had evidence of PD during chemotherapy (mean age: 57 years). Median survival of this subgroup was 4.8 months. None of them were stabilized with radiotherapy.

### Survival

7/34 (4/7 alive at the end of the study) were considered as long-term survivors (>18 months; range: 19-36 months). The mean age of long-term survivors was 56.4 years. Age was not a determinant of survival but 5/7 glioblastomas in long-term survivors were located in frontal or temporal lobes. 4 patients lived more than 2 years (range: 2.5-3 years). 3 patients had second-line chemotherapy.

Median time to progression after radiotherapy was 6.9 months for stable and responding patients. Mean survival duration was 14.1 months for the whole group (10.9 months in the 27 deceased patients), with median survival 9.6 months (Fig. 1). Mean and median survival rates were different because of long-term survivors. Median survival rates at 6 and 12 months were 85% and 38%, respectively.




### Toxicities

Toxicity was not high and mainly haematological due to the chemotherapy given. Neutropenic fever was rare and no intracranial haemorrhages or treatment-related deaths were noted. Nausea, vomiting and peripheral neuropathy were also rare. No patient had deep venous thrombosis or pulmonary emboli requiring anticoagulation.

Haematological grade III-IV toxicity was observed for 9/34 patients (26%). Grade III-IV leucopenia appeared in 5/34 patients without neutropenic fever. Grade III-IV thrombopenia was observed in 24/262 cycles but no patient required platelet transfusion. Nausea and vomiting (grade 1) occurred in 65% of patients despite treatment with intravenous ondansetron. Seventy percent of patients complained of asthenia and anorexia for 1 week following the course and these symptoms increased with the number of courses. A cisplatin-induced peripheral neuropathy occurred in 5 patients. This condition was generally mild and did not require discontinuation of chemotherapy.

**Radiotherapy**

No interruptions to RT were necessary based on our predetermined toxicity criteria. However, unscheduled interruptions (all <3 days) occurred because of bad weather conditions or technical problems with RT equipment for 5 patients and a seizure in 2 patient.

**Table 2: Selected studies of neoadjuvant chemotherapy in the treatment of high-grade gliomas**

| *Reference* | *CT* | *Histology* | *n.* | *RR (%) (CR/PR/SD/PD)* | *OS (months)* | *DFS (months)* |
|---|---|---|---|---|---|---|
| Gruber *et al.*, 1998 (17) | CBDCA | glioblastoma | 25 | NR | 19 | 8.5 |
| Rajkumar *et al.*, 1998 (18) | cisplatin, BCNU, VP-16 | malignant glioma | 16 | 0/22/77/11 | 14 | 13 |
| Jeremic *et al.*, 1999 (19) | CBDCA, VP-16 | malignant glioma | 45 | 0/24/65/11 | 14 | 12 |
| Grossman *et al.*, 1997 (20) | BCNU, cisplatin | malignant glioma | 52 | 0/42/53/4 | 13 | NR |
| Dazzi *et al.*, 2000 (21) | BCNU, cisplatin | malignant glioma | 13 | 23/30/NR/NR | 9 | NR |
| Gilbert *et al.*, 2000 (22) | cisplatin, BCNU | glioblastoma | 41 | 2.4/24/44/29.6 | 9.3 | 5.2 |
| Vin˜ olas *et al.*, 2002 (23) | CBCDCA, CFM | malignant glioma | 17 | 0/6.5/13.5/80 | 7.6 | NR |
| Fetell *et al.*, 1997 (24) | paclitaxel | glioblastoma | 33 | 0/0/12/88 | 12 | NR |
| Balan˜ a *et al.*, 2001 (25) | cisplatin, TMZ | glioblastoma | 14 | 11/56/22/1 | NR | NR |

CT= chemotherapy regime, n= number of patients evaluable, CR = complete response, PR = partial response, SD= stable disease, PD= progressive disease, OS =overall survival, DFS= disease-free survival, CBDCA=carboplatin, VP-16= etoposide, CFM= cyclophosphamide, TMZ = temozolamide, NR= not reported

**4.Discussion:**

In the last two decades there was much attention focused to optimize the best sequence of chemotherapy and radiotherapy to enhance the outcome. When we designed this study, there were several hypotheses to support the interest in pre-radiotherapy sequencing of chemotherapy. First, in several preclinical models, the response to sublethal ionizing irradiation of malignant glioma cells was by upregulating the cell survival pathway, which apparently secured them from death. These activated pathways also cause resistance to subsequent chemotherapy (9, 10). Second, radiation injures the vascularity of the tumor directly and may further decrease its perfusion (11). At the same time the changes in the tumor microvasculature induced by surgery leading to increase in the permeability of the blood brain barrier also increases the effectiveness of the given chemotherapy (12). Third, theoretically radiotherapy may lead to increase in the local interstitial pressure which may diminish the local perfusion (13, 14). Finally, using chemotherapy regimens that contains cisplatin prior to radiotherapy has an additional benefit of causing radiation sensitization, as cisplatin can persist in the tissue long time after administration (15). Due to the above reasons, many trials started to test the value of chemotherapeutic regimens before radiotherapy and it has been argued to be the optimal setting to identify active (and inactive) treatment protocols without the confusing effect of radiotherapy, both in term of reduction in efficacy (due to radiation induced resistance) and positive value (owing to synergy with radiotherapy).

The inverse observation that delaying radiotherapy doesn't cause decrease in the survival rates, is also important. In fact delaying radiotherapy has some possible advantages. This technique is potentially very useful in clinical trials where the delay of radiotherapy can allow to efficiently asses the response to chemotherapeutic agents. When radiotherapy is delayed it is possible to evaluate the response rate to chemotherapy itself. In contrast if chemotherapy is given simultaneously with radiotherapy, it is difficult to evaluate the response rate and the only measure of efficacy is the survival. Using response as an endpoint allows much more efficient initial determination of whether a drug

deserve further study than does assessment of survival (16). In our study it was decided to administer neoadjuvant cisplatin and vincristine, two agents widely used for treatment of high-grade gliomas, with a synergistic effect *in vivo* and in vitro. In addition, each has a different toxicity profile so this allowed them to be given in combination.

We can consider our patients to be a poor prognostic group due to the fact that patients with class IV and V of the RTOG prognostic groups are predominant, their median survival rates are 9.6 months and their 2 years survival rates are only 10%-15%. After analyzing the pretreatment prognostic factors in our study, it showed statistical significance for well established clinical prognostic factors as extent of surgery and location of the tumor. However, any generalization is difficult to assess due to the small number of patients included. Of note, another factor that showed statistical significance (as would expected) was the radiological presence of necrosis and ring enhancement which is a typical radiological feature of glioblastoma.

The response rate observed in phase I and II trials with neoadjuvant chemotherapy compared to our trial showed various response ranges (17-25) from the 0% observed with paclitaxel in the study by Fetell *et al.* (24) to the 42% observed with continuous infusion of cisplain and BCNU in the study by Grosman *et al.* (20). The use of cisplatin vincristine as chemotherapy regimen in our study probably reflected on our low response rate, two chemotherapy agents with lower intrinsic activity than temozolamide and nitrosureas (Table 2). However in spite of these different response rates, none of these studies with chemotherapy prior to radiotherapy, including our own, seem to adversely affect survival in these patient populations compared to similar population groups treated in the standard manner.

Only a phase III trial has been published with regard to the value of neoadjuvant chemotherapy. Grossmann et al., on behalf of the Eastern Cooperative Oncology-Group/ Southwest Oncology Group, randomized 219 patients with newly diagnosed GBM between standard adjuvant BCNU and radiotherapy and neoadjuvant chemotherapy with 72-h infusion of BCNU and cisplatin for 3 cycles, prior to radiotherapy, as in the previous phase II studies (26). The results were frustrating. Twenty-four percent of patients progressed during chemotherapy. No differences were seen with regard to OS (11.2 versus 11 months) or 1-year survival rates (45 versus 44%). Toxicity was higher in the experimental arm. The authors concluded that the high RRs observed in the phase II setting did not translate in a meaningful survival benefit.

High-grade gliomas, and especially GBM, are known to be aggressive diseases, and their prognosis depends more in large part in a series of well-known clinical prognostic factors than in any new treatment modality that can be offered to these patients (27). Aside from adjuvant radiotherapy whose value is well proven, progress with chemotherapy has been little. The value of adjuvant chemotherapy is shown basically in two meta-analyses (28, 29), which showed a modest survival benefit with adjuvant treatment with BCNU, one of them only in young patients, and a slight increase in the number of long-term survivors. There are no known characteristics that can foretell which patients will profit from its use (30). Also, in phase III trials the toxicity of combination adjuvant chemotherapy can be substantial (65% of patients in the Grossmann trial suffered grade 3–4 toxicity) and its indication must be weighed carefully. Moreover, the recent Medical Research Council randomized study in high-grade gliomas and showed no benefit to adjuvant PCV together with radiotherapy, has shed more doubts on the real benifit of adjuvant chemotherapy in glioblastoma (31). However, the preliminary recent findings by Stupp (32) on the benefit of standard radiotherapy alone compared to early concomitant and adjuvant temozolamide seem to show that the highest advantage of chemotherapy could be seen with its early use after surgery, rather than its use after radiotherapy. In this regard, neoadjuvant chemotherapy may offer some theoretical advantages, especially with regard to discovering more active agents, but its real value and possible advantages still have to be determined.

Thus, it seems unclear to identify the value of neoadjuvant chemotherapy. Although there are wide variations between response rates depending on the chemotherapy used, there is no significant advantage (or disadvantage) has been observed in relationship to survival compared to controls with standard treatment with adjuvant chemotherapy. It seems that, more than the benefit of neoadjuvant chemotherapy, what is still in question is the benefit of chemotherapy in general in the first-line treatment of high-grade gliomas.

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