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Clinical report

Pre-irradiation semi-intensive chemotherapy with carboplatin and cyclophosphamide in malignant glioma: a phase II study

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We undertook a phase II trial in 17 patients with malignant glioma and large measurable disease to assess response rate and survival with pre-irradiation chemotherapy, using higher doses than standard, trying to improve the outcome. Patients characteristics were: male/female 10/7, age 49 (range 23–59), median Karnofsky index 90% (range 70–100), glioblastoma multiforme/anaplastic astrocytoma 14/3. Treatment consisted of 2 cycles of carboplatin 200 mg/m^2 days 1–3 (or AUC $\times$ 8, total dose) plus cyclophosphamide 1000 mg/m^2 days 1–3. One partial response (6.5%) and two stabilizations (13.5%) were observed after pre-irradiation chemotherapy. Twelve out of 15 patients (80%) progressed after chemotherapy. Median survival time was 7.6 months and the survival at 1 year was 33%. Main toxicity was hematologic in the first cycle: neutropenia grade 4 in 100%; thrombocytopenia grade 4 in 73% and grade 3 in 27%; anemia grade 3 in 7%; in the second cycle: neutropenia and thrombocytopenia grade 4 in 100% and anemia grade 3 in 50%). No toxic death was related to treatment. This regimen showed limited activity in malignant glioma with large residual disease after surgery or biopsy. [© 2002 Lippincott Williams & Wilkins.]

Key words: High-dose, malignant glioma, pre-irradiation chemotherapy.

Introduction

Survival of patients with malignant gliomas is poor despite significant advances during the past decade in neuroimaging, surgery, radiation therapy and chemotherapy. Adults with newly diagnosed glioblastoma have a median survival of 6–12 months and are rarely cured. It would appear that pretreatment prognostic factors influence outcome more than modifications in therapeutic approaches.[1] The value of chemotherapy as adjuvant to surgery and radiotherapy is modest,[2,3] with a moderate increase in long-term survivors.[4] The drugs considered the most active against brain tumors are mainly those possessing alkylating activity; these drugs display a directly proportional dose–response effect.[5]

Carboplatin and cyclophosphamide are non-crossing alkylating agents with demonstrated activity against gliomas.[6–14] They have logarithmic dose–response curves *in vitro*, a synergistic mechanism of action and tolerable non-overlapping toxicities. Chemotherapy at higher doses seems to be a reasonable strategy to overcome the shortcoming of standard treatment.[15] Furthermore, pre-irradiation chemotherapy provides the best opportunity to evaluate the responses without the superimposed effect of radiotherapy.

We undertook a phase II trial to assess the response rate and survival of pre-irradiation chemotherapy with doses higher than standard in a subgroup of patients with high-grade gliomas with large measurable disease after surgery.

Materials and methods

Patient population

From January 1996 to October 1998, 17 patients diagnosed with glioblastoma multiforme (GBM) (n=14) and anaplastic astrocytoma (AA) (n=3) in two institutions, with gross measurable disease after

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surgery (mean greater diameter 5 cm, range 2.5–6 cm) measured by computed tomography (CT) scan or magnetic resonance imaging (MRI), were treated with carboplatin and cyclophosphamide at higher doses than standard.

All patients had histological confirmation of supratentorial high-grade glioma according to the Modified Ringertz classification.[16] Other eligibility criteria were: age <60 years, Karnofsky performance status (KPS) $>60\%$; and normal hematologic counts (WBC count $>4 \times 10^9$/l, platelet $>100 \times 10^9$/l), renal (creatinine concentration <1.4 mg/dl) and hepatic (bilirubin level <1.3 mg/dl) function; all had no prior chemotherapy or radiotherapy.

Patients were enrolled after giving informed consent. Investigators at both participating institutions were required to obtain approval from their individual institutional review boards and from the National Health Service.

Treatment schedule

Two cycles of carboplatin 200 mg/m^2/day (days 1–3) (or AUC=8, total dose, divided over 3 days based on the Calvert formula) and cyclophosphamide 1000 mg/m^2/day (days 1–3) were planned before standard radiotherapy. Granulocyte macrophage colony stimulating factor (G-CSF) 5 μg/kg/day was administered from day 2 after chemotherapy until WBC $>3 \times 10^9$/l. Platelet and packed red cell transfusions were given to maintain a platelet count $>20 \times 10^9$/l and hemoglobin level >80 g/l, respectively. Oral antibiotics were started at the time of neutropenia and neutropenic fever was treated with appropriate i.v. antibiotics when necessary.

Radiation was given at 2 Gy per fraction (five fractions per week) to the isocenter for a total dose of 60 Gy. The target volume encompassed the contrast enhancement mass plus a 2 cm margin of normal brain tissue. Megavoltage techniques with multiple field ports were designed.

After standard radiotherapy, BCNU (dose 200 mg/m^2 every 8 week, maximum 6 cycles) was administered in patients with a KPS $>60\%$ in which the CT scans or MRI showed residual tumoral mass.

Treatment modifications

Two cycles of chemotherapy separated between 4 and 6 weeks were planned if stabilization or response was observed after the first cycle. Delays in the administration of the second cycle were allowed until 6 weeks, but no chemotherapy dose modifications were permitted.

Measurement of response, survival and toxicity

Within 14 days of the initial surgical procedure, each patient had a baseline evaluation consisting of physical examination, neurological examination, determination of KPS, complete blood count and serum chemistries. All baseline evaluations were repeated prior to the second cycle and 1 month after finishing radiotherapy.

Contrast-enhanced CT scan or MRI was performed in the first 5 days after surgery to ensure that contrast enhancement was secondary to the residual tumor rather than to surgical changes.[17,18] Radiological response was assessed 4 weeks after each chemotherapy cycle and 1 month after radiotherapy. The doses of dexamethasone, used to control brain edema, were kept as constant as possible to ensure that changes in the CT scan or MRI were not related to changes in glucocorticoid doses. To assess the response, the same initial neuroimaging technique was used.

Response was assess according to McDonalds criteria,[19] and hematological and non-hematological toxicity was graded following WHO criteria.[20]

Statistics

The planned number of patients included in the protocol would have a statistical power of 80% based on $\alpha=0.05$ to detect a minimal probability of response of 30%.[21] Survival was determined from the date of surgery to death or last visit. Survival analysis was based on the Kaplan–Meier test.[22]

Results

Patients characteristics are shown in Table 1. Two patients were not assessable either for response or survival—one died before starting treatment and the other 12 h after the administration of the first cycle of chemotherapy, both from progression of the disease. In total, 22 cycles of chemotherapy were given.

After the first cycle of chemotherapy seven patients progressed and eight stabilized. One of the patients who stabilized refused further treatment and the other seven patients received a second cycle of

Table 1. Patient characteristics

Male/female	10/7
Age (years) [median (range)]	49 (23–59)
Karnofsky (%) [median (range)]	90 (70–100)
Histology	
glioblastoma multiforme	14
anaplastic astrocytoma	3
Surgery	
biopsy	12
partial resection	5

chemotherapy. One achieved a partial response (6.5%), another stabilized and five progressed. After two cycles of chemotherapy, 12 out of 15 patients (80%) progressed. The patient with a partial response had GBM and was free of tumor progression for 5 months.

All patients but one started radiotherapy and 11 completed treatment. Response after radiotherapy showed five stabilizations and six progressions. Six patients, who presented a KPS >60 after radiation treatment, received BCNU.

Median survival time was 7.6 months and the survival at 1 year was 33%.

Main toxicity was hematologic: in the first cycle, neutropenia (grade 4) was detected in 100%, thrombocytopenia grade 4 in 73% and grade 3 in 27%, and anemia grade 3 in 7%. Median neutrophil and platelet recovery were reached on day 11 (8–17) and 13 (0–17), respectively, and median numbers of days with neutrophils $<0.5 \times 10^9$/l and platelets $<20 \times 10^9$/l were 6 (2–10) and 1 (0–8), respectively. The median number of days that G-CSF was given was 11 (range 8–15). Three patients required packed red cell transfusions, median number 1 (range 0–2) and nine patients received pool platelet support, median number 1 (range 0–3). At second cycle hematologic toxicity was slightly superior with neutropenia and thrombocytopenia grade 4 in 100% and anemia grade 3 in 50%. Median neutrophil and platelet recovery were reached on day 12.5 (10–21) and 10 (9–12), respectively, and median numbers of days with neutrophils $<0.5 \times 10^9$/l and platelet under 20×10^9/l were 7 (4–13) and 3 (1–14), respectively. Median number of days receiving G-CSF was 13.5 (range 10–21). At this time five patients required packed red cell transfusions (median 1, range 0–3) and all patients had to be given pool platelet support. Nine patients experienced febrile neutropenic episodes requiring broad-spectrum antibiotics (median number of days for febrile patients was 10, range 6–13). Bacteriemia was documented in two patients (*Escherichia coli* and coagulase-positive *Staphylococcus aureus*). Other toxicities were mucositis grade 3 in one patient and neurotoxicity grade 2 in another. No toxic deaths were observed.

Discussion

Currently, no therapy has been proven to be superior to surgery, radiation and chemotherapy (nitrosourea-based) in patients with high-grade gliomas. Since the outcome for these patients remains poor with standard therapy, other innovative approaches to treatment are needed.

The optimal sequence of chemotherapy and radiation in the treatment of high-grade gliomas has not yet well defined. It seems that there may be some biological advantages in the administration of chemotherapy prior to radiotherapy, such as the possibility of assessing the responsiveness of these tumors to chemotherapy alone and the probability of improvement in drug delivery because tumor blood vessels have not been damaged by the radiation. The major risk to this approach is the delay of radiation therapy. In our study we performed a MRI or CT scan image after each cycle and patients who progressed according to the McDonald criteria were given radiation treatment immediately in order to minimize this risk. A few studies have analyzed the administration of chemotherapy prior to radiotherapy,[23–29] but none in patients with such poor prognostic factors. The response rate varies from 42% partial responses in the study of Grossman[24] where patients received continuous infusion of carmustine and cisplatin to 0% published by Fetell[26] with paclitaxel in 31 assessable patients. None of these studies with chemotherapy prior to radiotherapy adversely affected survival in this patient population.

Cumulative data from high-dose chemotherapy in recurrent gliomas suggest that although the median survival does not differ significantly when compared with patients treated with standard therapy, there are a few long-term survivors even in heavily pretreated patients.[30–32]

In our group of patients treated with chemotherapy prior to radiotherapy, using higher doses than standard, one partial response was observed. The median survival time for the whole series was 7.6 months and only one patient with anaplastic astrocytoma survived for more than 3 years. Unfortunately, the results came short of what was expected. Carboplatin, at standard doses, has been found to be an active regimen even in recurrent glioma.[9,10] Recently, a new way to increase the delivery of

carboplatin in tumors has been by adding RMP-7, a synthetic bradykinin B2 receptor antagonist, which selectively and transiently increases the permeability of the blood–brain barrier. The authors found that RMP-7 and carboplatin have significant activity in recurrent malignant glioma following radiotherapy.[13] However, our study using carboplatin at higher doses than standard does not show the same results. This discrepancy could be partially due to the large residual disease of our malignant glioma patients. It is well known that residual disease after surgical procedure is an important variable related to survival and also to treatment response.[13,33] An analysis of large numbers of patients treated on Radiation Therapy Oncology Group trials has suggested that the median survival of patients with prognostic factors similar to those described in our study population was approximately 8.5 months.[1] This is not so different than the survival rate of patients in the present study.

The study reported here and others[24,34] have demonstrated that it is possible to administer chemotherapy prior to radiotherapy without an adverse impact on survival in adults with high-grade astrocytomas. This regimen showed limited activity in malignant gliomas with gross residual disease. More active drugs and schedules have to be investigated in order to improve the poor outcome of this subgroup of patients.

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