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Carboplatin and Etoposide for Recurrent Malignant Glioma Following Surgical and Radiotherapy Failure: A Clinical Study Conducted at the Northern Israel Oncology Center

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Background and Objectives: We conducted a phase II study using carboplatin and etoposide on patients with recurrent malignant glioma to investigate tumor response.
Methods: From January 1995 to March 1997, 21 patients with recurrent malignant glioma were treated with a carboplatin (300 mg/m^2, day 1)/etoposide (100 mg/m^2, days 1–3) regimen every 3–4 weeks. The following radiologic parameters were evaluated: tumor size, central lucency, degree of contrast enhancement, and mass effect. No patient had received chemotherapy previously. Dose escalation corresponded to hematologic tolerance and to general and neurologic performance status. Most patients were treated postoperatively with involved field radiotherapy followed by a boost to the tumor area, as defined on the presurgery computed tomography scan or on magnetic resonance imaging. Mean interval to introduction of chemotherapy was 8.8 months (range, 7–36 months). Patients received a mean of four cycles [range, 2–8 cycles].
Results: Only 2 patients showed moderate radiological response, while 12 patients died of progressive disease. Mean time to progression following discontinuation of chemotherapy was 5.8 months (range, 1–11 months). The other patients survived with persistent disease and are being treated palliatively. Toxicity was manageable (1, neutropenic sepsis; 1, thrombocytopenia (45,000/mm^3); 2, temporarily elevated transaminase level; 2, steroid-induced erosive gastritis).
Conclusions: This phase II regimen proved to be ineffective in recurrent malignant glioma. Further studies incorporating innovative drug regimens and schedules are warranted.
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KEY WORDS: **carboplatin; etoposide; recurrent brain glioma**

INTRODUCTION

The treatment of recurrent cerebral glioma remains palliative, with reasonable responses being infrequent. With a variety of chemotherapy regimens—many of

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which include nitrosurea derivatives—combined response and stabilization rates of 20–65% were achieved, albeit with a median response duration of 6–11 months, in glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA) patients [1,2].

Carboplatin (CBDCA) is a second-generation cisplatin (CDPP) analog with similar but not identical oncolytic activity and no disabling side effects, such as severe emesis, renal damage, hearing loss, or peripheral neuropathy. Studies of in vitro chemosensitivity of brain tumors to CDDP and CBDCA show that CBDCA may have better antitumor activity than CDPP [3,4]. Single agent carboplatin achieved a 40–50% response rate with a median time to progression of 11–19 weeks. Combining carboplatin with etoposide (VP-16) showed a synergistic activity against a number of experimental in vivo and in vitro systems. Clinically, this regimen has shown comparable results with other series using platinum-based regimens [3–5].

We present our results in 21 patients with recurrent malignant gliomas treated with carboplatin/VP-16 (CE) within the framework of a phase II study.

PATIENTS AND METHODS

All patients entered in this study were treated and followed at the Northern Israel Oncology Center. From January 1995 to March 1997, 21 patients with recurrent glioma were treated with CE chemotherapy regimen. Eligibility criteria included: 1) Karnofsky performance status $\geq$ 60%; 2) histologically proven malignant glioma; 3) evidence of recurrent or progressive disease documented by contrast enhanced computerized tomography [CT] scan and magnetic resonance imaging [MRI]; 4) failed postoperative radiotherapy; 5) measurable disease; 6) adequate bone marrow [white blood cell count $\geq$ 3,000/mm^3, platelet count $\geq$ 90,000/mm^3]. Audiogram and normal liver and renal functions were required before the introduction of therapy. In some patients, Thallium-SPECT examinations were performed before and during the chemotherapy, in addition to CT scan and MRI response assessment follow-up. Before the first treatment, all patients underwent a neurologic examination by an experienced neuro-oncologist (TS-Z), with determination of performance status. Written informed consent was signed by all patients.

The chemotherapy protocol consisted of carboplatin 300 mg/m^2 intravenously (IV) on day 1 and etoposide (VP-16) 100 mg/m^2 IV on days 1–3, with adequate hydration and diuresis. Cycles were repeated every 3 to 4 weeks. All patients were given the lowest steroid dose required for neurologic stability during treatment. A complete blood count was taken every week, with a full biochemical profile, physical examination, and neurologic assessment performed before every new cycle.

Contrast enhanced CT scan and/or MRI scan was obtained every 7 to 8 weeks. The following parameters were evaluated: tumor size, central lucency, degree of contrast enhancement, surrounding edema, mass effect, and shifts of intracerebral structures. Measuring of diameters has not been satisfactory because of the unusual shapes and infiltrating tumor characteristics. Clinical response criteria followed the clear guidelines of Levin and Prados [6]. Due to the well-known extreme scarcity of complete remission, the term of objective response (decrease in size of tumor by $\geq$ 50%, stable corticosteroid dose, improvement from pretreatment status) was added to the response criteria.

Toxicity criteria were evaluated with World Health Organization (WHO) guidelines. Off-study criteria included: 1) progressive disease, 2) rapid physical and/or neurological deterioration, and 3) unacceptable toxicity.

TABLE 1. Characteristics of 21 Patients With Recurrent Malignant Gliomas

No. of patients	21
Male:Female	1:1
Age	
Mean	46
Range	18–64
Surgical procedures	
Stereotactic biopsy	4
Subtotal resection	12
Gross total tumor resection	5
Total radiation dose (cGy)	
Involved field	
Mean	5,090
Range	4,000–6,540
Boost	
Mean	1,800
Range	1,500–2,000
Whole brain irradiation	
Mean	4,050
Range	3,500–4,600
Histological characteristics	
Glioblastoma multiforme	10
Anaplastic astrocytoma	8
Gemistocystic astrocytoma	2
Anaplastic astro-oligodendroglioma	1
Interval to chemotherapy (months)	
Mean	8.8
Range	1–36
Cycles of chemotherapy	
Mean	4
Range	2–8

RESULTS

Patient characteristics are seen in Table I. One patient developed glioma 1.5 years after being in complete remission from a removed $T_2N_0M_0$ [stage 1] squamous cell lung cancer. He did not receive any postoperative treatment to the lung.

The overwhelming majority of tumors were localized in the hemispheric regions, mostly in the temporoparietal/frontal lobes. Only one patient with radiologically

confirmed brain stem glioma did not undergo any invasive surgical procedure. All other patients underwent a wide range of surgical approaches.

All patients received radiation therapy postoperatively. Radiation therapy was given with a 6 MV linear accelerator (Varian 1800). Most patients received involved field irradiation; the initial target volume included the preoperative radiologically enhanced tumor mass and the surrounding area of brain edema, with a 2–3-cm margin, following a cone-down boost directed to the contrast enhanced tumor area.

Mean interval to the commencement of chemotherapy from the completion of radiotherapy was 8.8 months. Two patients, who underwent surgical reexcision of residual tumor 4 and 6 months after completion of their radiotherapy program, started the scheduled chemotherapy 12 and 16 months after the end of their radiotherapeutic treatment, respectively. Two patients with AA enjoyed a long symptom-free interval [24 and 36 months] before tumor progression and introduction of chemotherapy.

Two patients showed moderate radiological response following three cycles of chemotherapy, one for 3 months and one for 4 months. Repeat MRI exhibited reduction in tumor size and contrast media enhancement. Consequently, chemotherapy continued for a further three and five cycles until clear tumor progression. One patient demonstrated response following three cycles of chemotherapy, but he deteriorated rapidly and was unsuccessfully reirradiated.

Twelve patients died of progressive disease. Mean time to progression following cessation (or discontinuation) of chemotherapy (compatible with tumor progression) was 5.8 months [range, 1–11]. Seven patients are alive with disease [mean follow-up of 7 months] and are being treated palliatively. Two patients with persistent disease but no severe physical or neurological dysfunction are being treated with oral procarbazine (Natulam®). The histologic subtype did not have any influence on the response rate or rapidity of progression.

Toxicity was manageable. Dose escalation was performed on one patient without myelotoxic side effects. One patient was complicated by neutropenic sepsis following two cycles of chemotherapy. This patient, following stereotactic biopsy, was treated in another hospital with whole brain irradiation (35 Gy), boost to tumor area (26 Gy), and high dose tamoxifen (240 mg total dose) for several months until clear progression. He recovered uneventfully from the sepsis but died 2 months later due to progressive disease.

One patient developed thrombocytopenia [45,000/mm^3], two patients had temporarily elevated transaminase levels, and two patients had steroid induced erosive gastritis. Treatment was delayed for 1 to 3 weeks in these patients. No renal side effects or neurotoxicity occurred.

DISCUSSION

Clinical trials have documented the efficacy of drugs such as nitrosurea derivatives, procarbazine, and platinum analogues in recurrent brain gliomas. Studies reviewing this efficacy, mostly retrospective, have documented response rates of 17–92%, with time to progression from 23 to 78 weeks and a median survival of 6 and 11 months for GBM and AA [1–3,7]. However, such studies have included only a small number of patients and suffer from a lack of uniformity in the response criteria. Larger scale reviews are usually in the form of a summary of many small phase II studies with varying inclusion criteria. It is reasonable, therefore, to present a large single center's experience of chemotherapy in patients with recurrent glioma where the criteria for patient selection are relatively uniform. We still await such a patient accrual.

Generally, the assessment of the efficacy of conventional and new treatment modalities is complicated by the difficulty of evaluating responses on conventional computerized tomographic scans or even magnetic resonance imaging and, simply, by the difficult assessment of clinical response in patients with neurological deficits. No correlation can be defined by using objective solid non-brain tumor response criteria in malignant gliomas [8,9]. An alternative method of assessing tumor response can be the PET analysis, which can complement the unsatisfactory volumetric estimation of disease extent, as exhibited through modern, albeit conventional, imaging analysis.

Even the moderate increases in response rates, as demonstrated with platinum-analogue-based chemotherapy, did not improve long-term survival. Carboplatin, given as a single agent at a dose rate of 400–525 mg/m^2 every 4 weeks, yielded a total objective response rate (partial/minimal response and stable disease) of 48.3%, but only four patients [14%] had an objective response with a median response duration of 61.5 weeks [3]. Patients with AA showed a better response to carboplatin than did those with GBM. This is consistent with results in other chemotherapy studies [4,5,10]. In the study of Jeremic et al. [5], an overall response rate (partial response and stable disease) of 53% was achieved in patients with recurrent glioma treated with carboplatin/VP-16, and only 21% of patients achieved objective responses and no complete remission was exhibited. Increasing the platinum-analogue dose, adding VP-16 (known for its synergistic action with platinum-based agents) and ifosfamide could increase the rate of objective responses at the expense of increased toxicity [11]. Even the use of autologous bone marrow transplantation with high-dose chemotherapy (mainly BCNU) could not achieve defin-

able gains over conventional dose nitrosurea therapy. Neither high-dose thio-tepa nor etoposide has shown remarkable activity against recurrent brain gliomas [12].

In conclusion, our poor results should warrant innovative studies and experimental drugs and drug regimens to explore various dose schedules and modalities in combating recurrent gliomas. Furthermore, careful patient selection based on prognostic factors and rigorous response criteria should be essential elements of every study.

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