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Phase II study of a radiotherapy/etoposide combination for patients with newly malignant gliomas

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Abstract *Purpose*: Etoposide, a semisynthetic derivative of podophyllotoxine, is a topoisomerase II inhibitor. This drug is currently used in several types of human cancer. The aim of this study was to evaluate the efficacity and tolerance of a near-concurrent association of radiotherapy and etoposide for newly malignant gliomas. *Methods*: From May 1995 to December 1996, 30 malignant glioma patients were included in this phase II study; 16 patients underwent surgical tumor resection, and a stereotactic biopsy was performed in 14 patients. Standard cranial irradiation and six courses of etoposide (100 mg/m^2, ×days 1–3) were administered. The first course of etoposide was administered on days 1–3 of radiotherapy and was resumed in the week following the end of radiotherapy. Treatment was consolidated by further courses of etoposide every 4 weeks. *Results:* Only 26 patients could be evaluated for the purpose of our study. The median age was 60.1 years, and the median Karnofsky performance score (KPS) was 80.2. The rate of objective response for evaluable patients was 34.6%, and four complete responses (CR) and five partial responses (PR) were noted. The median survival (MST) was 12 months, and the average overall survival was 12.5 months. Hematological toxicity was mild, and grade 3 or 4 neutropenia (white blood cell count <1500/ml) was noted in three patients, without any sepsis or bleeding. *Conclusions*: The results obtained in this study are comparable to the best reported results on the combination of radiotherapy and nitrosoureas. The near-concurrent combination of radiotherapy and etoposide seems to be effective and well tolerated in the treatment of newly malignant gliomas.

Key words Chemotherapy · Concurrent radiochemotherapy · Etoposide · Malignant gliomas · Newly developed brain tumors

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Introduction

Primary tumors of the brain are challenging for clinicians and researchers. Because of their volume and/or their location, these tumors often cannot be treated by loco-regional methods such as surgery or radiotherapy [2]. The prognosis for patients with malignant gliomas remains very poor, and chemotherapy has done little to improve these results [8]. Although statistically significant, chemotherapy has failed to gain general acceptance, probably because the benefits appear marginal to many people [2, 8]. Several investigators have turned to phase II studies to identify new and more potent therapies.

Etoposide, a semisynthetic glucoside derivative of podophyllotoxin, is one of the most active and useful antineoplastic agents [11]. The inhibition of DNA topoisomerase II is now known to be a major mechanism in the action of etoposide, stabilizing the cleavable complexes which trigger cell death [11]. Etoposide is not usually used in the treatment of malignant glioma patients. However, a few clinical studies have used etoposide, usually in combination chemotherapy, as salvage therapy for recurrent gliomas, although its role in the treatment of gliomas as demonstrated by single-agent trials is less certain [22].

To determine whether etoposide is a therapeutic agent for malignant gliomas, we studied the in vitro sensitivity to etoposide of a panel of five characterized malignant glioma cell lines; the activity of topoisomerase II and its inhibition by etoposide were also studied in these cell lines [1]. The malignant glioma cell lines were found to be sensitive, and the median concentration inhibiting the number of cells by 50% (IC_{50}) was 8.76 μg/ml (range, 8–15.8 μg/ml) [1]. Topoisomerase II activity was homogeneous in glioma cell lines (average of 50% decatenation with 7000 cells), and topoisomerase II was shown to be the target of the etoposide [1]. We hoped that these interesting experimental results could be confirmed in vivo, and we therefore decided to develop a phase II clinical trial to test a near-concurrent combination of radiotherapy and etoposide in the treatment of newly malignant gliomas.

Materials and methods

Patients

From May 1995 to December 1996, 30 patients from whom informed consent had been obtained were included in a phase II clinical study. All patients had a histologic diagnosis of supratentorial malignant glioma (grades 3 and 4) based on the Daumas-Duport (Sainte-Anne–Mayo) classification. Their ages ranged from 18 to 72 years; they all had a minimum Karnofsky performance status (KPS) score of 60 with a life expectancy of at least 3 months and had normal pretreatment laboratory values (complete blood count, liver function tests, renal function tests, and electrocardiogram). None of them had received any prior chemotherapy or radiotherapy, and none was known to have any psychiatric disorder.

Therapeutic protocol

Patients underwent either minimal surgery with stereotactic biopsy or tumor resection, which was as extensive as possible. All patients also underwent partial brain irradiation to limited fields, and the treatment volume was determined by defining the volume of the contrast-enhanced tumor on a preoperative computed tomography (CT) scan with a 2-cm margin beyond the edema surrounding the tumor; a dosage of between 2 and 2.5 Gy per day was given five times per week for 5 weeks, up to a maximum of 50–55 Gy. Radiotherapy was started within the first 2–3 weeks following surgery. Patients who had undergone a complete tumor resection only received a total dose of 50 Gy. A single agent was used for chemotherapy: a topoisomerase II inhibitor, etoposide, given at 100 mg/m^2 for 3 consecutive days. The first course of etoposide was administered on days 1, 2, 3 of radiotherapy and was resumed in the week following the end of radiotherapy. Treatment was consolidated by a further four courses of etoposide at 4-week intervals. Supporting treatments included glucocorticoids at doses determined as a function of the patient's clinical status. The glucocorticoid dose was gradually reduced to finish in the sixth week after radiotherapy.

Response evaluation

Responses were evaluated according to the criteria presented by MacDonald et al. [16] based on clinical examination and measurements of the enhanced contrast area on CT scan. Both were performed every 8 weeks or more frequently if clinical changes seemed to warrant this. For patients who had undergone tumor resection, a cerebral CT scan was performed within 72 h of surgery to evaluate any residual tumor. For all patients, the first neuroradiological evaluation was performed at the end of the second course of chemotherapy. Complete response (CR) corresponded to a total regression of the enhanced contrast area, and partial response (PR) to a reduction in the enhanced contrast area by at least 50%. In both cases, clinical examination had to be normal or improved. Patients received no glucocorticoids when in CR, and stable or reduced doses in PR. Progressive disease (PD) corresponded to an increase of 25% or more in the enhanced contrast area in patients with stable or progressive neurological deficit, usually requiring increased doses of glucocorticoids.

Study objectives and end points

Our objective was to evaluate overall survival (OS), the time to tumor progression (TTP) in patients with malignant gliomas, and the toxicity of chemotherapy, using the National Cancer Institute common toxicity scale; dose reductions were allowed based on the grade and the type of toxicity. Blood counts were obtained every 2 weeks throughout the study. The chemotherapy dose was reduced to 50% on subsequent cycles if the leukocyte or platelet counts were 1000–1500 mm^3 or 99,000–75,000 mm^3, respectively, and stopped if these values were lower than 1000 mm^3 or 75,000 mm^3, respectively.

Statistical analysis

TTP was measured from the date of surgery until the tumor progression was documented by X-ray. Survival time was defined as the period between the date of surgery and the date of death, regardless of whether its cause was related to the malignant glioma. OS and TTP were calculated using the Kaplan-Meier method [5]. Differences in survival were tested for statistical significance using the log-rank test ($P \leq 0.05$).

Results

Patient characteristics

We treated 30 patients (nine women and 21 men) with malignant gliomas (seven grade 3 and 23 grade 4). The median age was 60.1 years (range, 34–72 years), and the median KPS was 80.2 (11 patients had a KPS greater than or equal to 85). Sixteen patients had undergone surgical resection (53.4%), including ten total macroscopic tumor resections (no contrast enhancement at CT scan performed within 72 h of neurosurgery). For the 14 remaining patients, a stereotactic biopsy was carried out (46.6%). Only 26 patients were evaluated for the objectives of this study (four surgical patients were eliminated).

Response to chemotherapy

The overall MST was 12 months, with 15.4% of patients alive at 18 months and 4% alive at 24 months (Fig. 1, Table 1). The mean survival of our population was 12.5 months. Those patients who had undergone tumor resection had an MST of 15 months versus only 8 months in the stereotactic biopsy patients (Fig. 2, Table 2). The difference between the survival times of the two groups was significant ($P = 0.04$). The mean survival was 14.6 months and 10.7 months, respectively, for the surgical

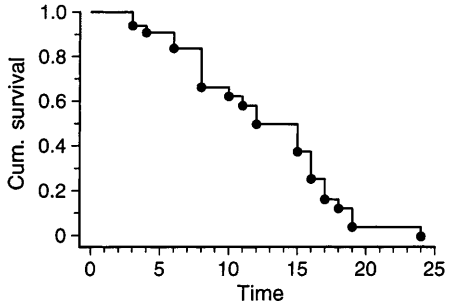

Fig. 1 Overall survival of all patients; mean survival time (MST) was 12 months. See also Table 1a, b

and stereotactic populations. The younger patients (< 50 years) had a MST of 16 months versus 10 months in older patients; the difference was significantly different ($P = 0.02$; Fig. 3, Table 3). Patients with a KPS of more than 80 had an MST of 15 months versus 8 months in patients with a KPS of less than 80 ($P = 0.01$; Fig. 4, Table 4). The overall median TTP was 7 months. The TTP of the 12 patients after tumor resection was 11 months and that of patients after stereotactic biopsy was 6 months.

Of the evaluable patients, nine patients (34.6%) responded to treatment, and four (15.4%) progressed within the first 3 months after starting treatment. Of the nine responding patients, there were four CR and five PR. Among the responding patients, four patients had grade 4 (two CR and two PR), and five had grade 3 (two CR and three PR). All but one of the responding patients had undergone a stereotactic biopsy. Overall, the therapy was well tolerated. Grade 3 or 4 neutropenia (white blood cell count < 1500/ml) was noted in three patients (four episodes). No course of chemotherapy was delayed. Only one patient received decreased doses of chemotherapy (75% of total dose). There were no treatment-related deaths, and no patients were removed from the study due to drug-related toxicity.

Discussion

There is only limited experience in the use of topoisomerase II inhibitors in the treatment of malignant gliomas [22]. Moreover, experimental data regarding the potential activity of etoposide in malignant glioma cell lines is rarely to be found in the international literature. The rationale of our protocol for investigating the use of etoposide beyond the 3-day standard intravenous dosage schedule is based on three major considerations: in vitro data, the radiosensitizing effect of etoposide, and clinical data:

Table 1a Kaplan-Meier survival table for the overall study population (see also Table 1b, Fig. 1)

Time (months)	Status	Cumulative survival	Cumulative failure	Survival SEM	Cumulative events	Cumulative censor	At risk
0		1.000	0.000	0.000	0	0	30
3	Uncensored	0.933	0.067	0.046	1	0	29
3	Uncensored	0.933	0.067	0.046	2	0	28
4	Uncensored	0.900	0.100	0.055	3	0	27
6	Uncensored	0.833	0.167	0.068	4	0	26
6	Uncensored	0.833	0.167	0.068	5	0	25
6	Censored	0.833	0.167	0.068	5	1	24
8	Uncensored	0.660	0.340	0.088	6	1	23
8	Uncensored	0.660	0.340	0.088	7	1	22
8	Uncensored	0.660	0.340	0.088	8	1	21
8	Uncensored	0.660	0.340	0.088	9	1	20
8	Uncensored	0.660	0.340	0.088	10	1	19
8	Censored	0.660	0.340	0.088	10	2	18
8	Censored	0.660	0.340	0.088	10	3	17
9	Censored	0.660	0.340	0.088	10	4	16
10	Uncensored	0.618	0.382	0.091	11	4	15
11	Uncensored	0.577	0.423	0.094	12	4	14
12	Uncensored	0.495	0.505	0.097	13	4	13
12	Uncensored	0.495	0.505	0.097	14	4	12
15	Uncensored	0.371	0.629	0.096	15	4	11
15	Uncensored	0.371	0.629	0.096	16	4	10
15	Uncensored	0.371	0.629	0.096	17	4	9
16	Uncensored	0.247	0.753	0.086	18	4	8
16	Uncensored	0.247	0.753	0.086	19	4	7
16	Uncensored	0.247	0.753	0.086	20	4	6
17	Uncensored	0.165	0.835	0.075	21	4	5
17	Uncensored	0.165	0.835	0.075	22	4	4
18	Uncensored	0.124	0.876	0.066	23	4	3
19	Uncensored	0.041	0.959	0.040	24	4	2
19	Uncensored	0.041	0.959	0.040	25	4	1
24	Uncensored	0.000	1.000	0.000	26	4	0

SEM, standard error of mean

Table 1b Summary survival table (see Table 1a)

Observed (*n*)	Events (*n*)	Censored		Missing (*n*)	Invalid (*n*)
		(*n*)	(%)		
30	26	4	13.333	0	0

Censor variable, DVM

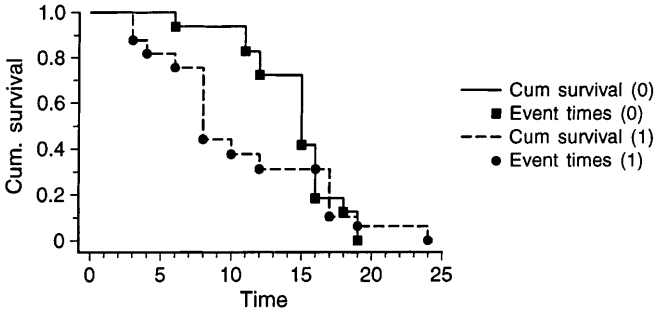

Fig. 2 Survival curves. The mean survival time (MST) for patients with tumor resection and for patients with stereotactic biopsy were 15 months and 8 months respectively ($P = 0.04$). See also Table 2a, b

– Our experimental study demonstrated that five malignant glioma cell lines were sensitive; the median concentration inhibiting the number of cells by 50% (IC_{50}) was 8.76 μg/ml [1]. Moreover, these glioma cell lines actually displayed homogeneous topoisomerase II activity, and this enzyme was effectively shown to be the target of etoposide [1].
– A small amount of experimental data has been published demonstrating etoposide to be a radiosensitizer and considering the resulting supra-additivity effect [10, 18]. Furthermore, this supra-additivity phenomena was proved with a human cancer cell line, a glioma cultured line [19].
– Only a few clinical trails have demonstrated the cytotoxic action of etoposide on malignant glioma tumors [6, 9, 22]. However, etoposide was not used as a single drug, and most of the studies used a combination of antineoplastic drug [3, 4, 13, 17, 20].

The rate of response and stabilization obtained with the most active drugs (casmustine, BCNU; procarbazine; and PCV) for the treatment of malignant gliomas fluctuates from 50% to 42% [1]. For *cis*-platin, the rate of objective response is 20% [1]. In the largest study of etoposide in recurrent malignant gliomas (22 patients), the objective response rate was 17%, and the disease stabilization rate an additional 17% of patients [22]. Fulton et al. [9], in their phase II study of prolonged oral therapy with etoposide in patients with recurrent malignant gliomas, found an objective response rate of 17% [9]. In this last study, there were 15 anaplastic astrocytomas and nine anaplastic oligodendrogliomas. For the other studies with etoposide, most of which combined etoposide with another antineoplastic drug, although suggesting that etoposide may be efficacious in combination with other drugs in malignant glioma

Table 2a Kaplan-Meier survival table for patients who underwent tumor resection (see also Table 2b, Fig. 2)

Time (months)	Status	Cumulative survival	Cumulative failure	Survival SEM	Cumulative events	Cumulative censor	At risk
0		1.000	0.000	0.000	0	0	14
6	Uncensored	0.929	0.071	0.069	1	0	13
6	Censored	0.929	0.071	0.069	1	1	12
8	Censored	0.929	0.071	0.069	1	2	11
8	Censored	0.929	0.071	0.069	1	3	10
9	Censored	0.929	0.071	0.069	1	4	9
11	Uncensored	0.825	0.175	0.115	2	4	8
12	Uncensored	0.722	0.278	0.139	3	4	7
15	Uncensored	0.413	0.587	0.157	4	4	6
15	Uncensored	0.413	0.587	0.157	5	4	5
16	Uncensored	0.413	0.587	0.157	6	4	4
16	Uncensored	0.310	0.690	0.148	7	4	3
17	Uncensored	0.103	0.897	0.098	8	4	2
17	Uncensored	0.103	0.897	0.098	9	4	1
19	Uncensored	0.000	1.000	0.000	10	4	0

SEM, standard error of mean

Table 2b Summary survival table (see Table 2a)

	Observed (*n*)	Events (*n*)	Censored		Missing (*n*)	Invalid (*n*)
			(*n*)	(%)		
0	14	10	4	28.571	0	0
1	16	16	0	0	0	0
Total	30	26	4	13.333	0	0

Censor variable, DVM; grouping variable, BSTX

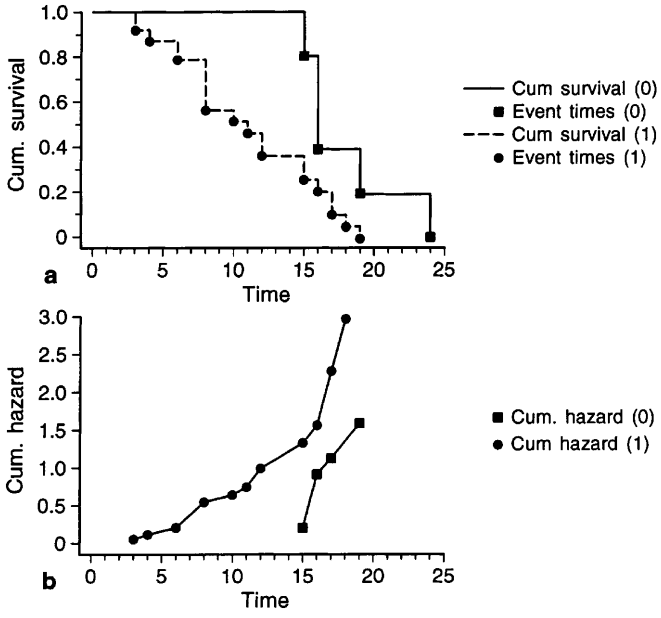

Fig. 3a, b Survival by age. **a** Survival curve. **b** Hazard curve. The median survival time (MST) for younger patients was 16 months versus 10 months for older patients ($P = 0.02$). See also Table 3a, b

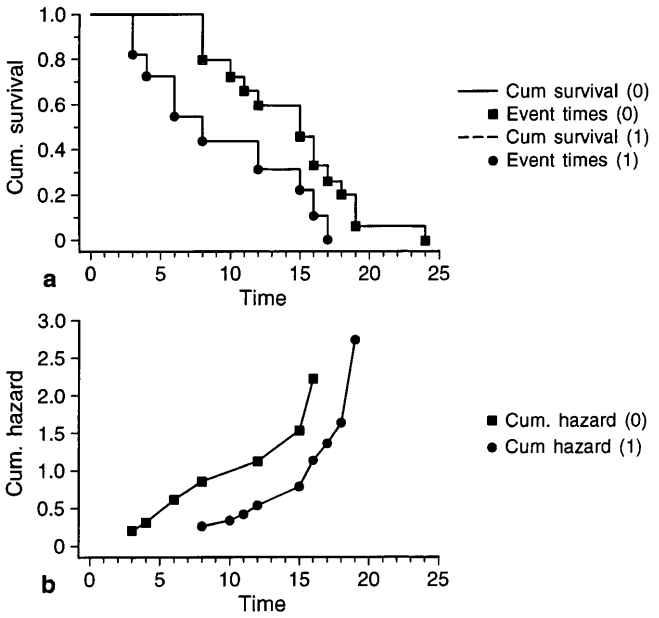

Fig. 4a, b Survival based on Karnofsky performance status (KPS). **a** Survival curve. **b** Hazard curve. The median survival time (MST) for patients with a KPS greater than 80 was 15 months versus 8 months for patients with a KPS of less than 80 ($P = 0.01$). See also Table 4a, b

patients, the data did not permit an assessment of the precise activity of etoposide [3, 4, 13, 17, 20]. The rate of objective response obtained in our study (34.6%) is comparable to what has been reported in these tumors with the most active chemotherapeutic agents in the international literature.

From their meta-analysis of phase III studies, Fine et al. [8] obtained an MST of 12 months for all populations, with glioblastomas and anaplastic astrocytomas considered together [8]. The nitrosoureas were the most frequently used chemotherapeutic in these studies [8]. Our results are comparable to those found in this meta-analysis. It is worth pointing out that the seven grade 3 astrocytoma patients in our series underwent a stereotactic biopsy. Malignant gliomas are known to be heterogeneous tumors, and a stereotactic biopsy may therefore lead to an underestimation of the correct histological grade of malignant gliomas. It is thus reasonable to consider our seven grade 3 tumors to be grade 4 tumors. For patients with glioblastomas, the most important series showed an MST of 6 months for the European Organization for Research and Treatment of Cancer (EORTC)

Table 3a Kaplan-Meier survival table for patients under 50 years (see also Table 3b, Fig. 3)

Time (months)	Status	Cumulative survival	Cumulative failure	Survival SEM	Cumulative events	Cumulative censor	At risk
0		1.000	0.000	0.000	0	0	6
8	Censored	1.000	0.000	0.000	0	1	5
15	Uncensored	0.800	0.200	0.179	1	1	4
16	Uncensored	0.400	0.600	0.219	2	1	3
16	Uncensored	0.400	0.600	0.219	3	1	2
19	Uncensored	0.200	0.800	0.179	4	1	1
24	Uncensored	0.000	1.000	0.000	5	1	0

SEM, standard error of mean

Table 3b Summary survival table (see Table 3a)

	Observed (*n*)	Events (*n*)	Censored		Missing (*n*)	Invalid (*n*)
			(*n*)	(%)		
0	6	5	1	16.667	0	0
1	24	21	3	12.500	0	0
Total	30	26	4	13.333	0	0

Censor variable, DVM; grouping variable, classed age

Table 4a Kaplan-Meier survival table for patients with a kamofsky performance status greater than 80 (see also Table 4b, Fig. 4)

Time (months)	Status	Cumulative survival	Cumulative failure	Survival SEM	Cumulative events	Cumulative censor	At risk
0		1.000	0.000	0.000	0	0	11
3	Uncensored	0.818	0.182	0.116	1	0	10
3	Uncensored	0.818	0.182	0.116	2	0	9
4	Uncensored	0.727	0.273	0.134	3	0	8
6	Uncensored	0.545	0.455	0.150	4	0	7
6	Uncensored	0.545	0.455	0.150	5	0	6
6	Censored	0.545	0.455	0.150	5	1	5
8	Uncensored	0.436	0.564	0.155	6	1	4
12	Uncensored	0.327	0.673	0.150	7	1	3
15	Uncensored	0.218	0.782	0.134	8	1	2
16	Uncensored	0.109	0.891	0.102	9	1	1
17	Uncensored	0.000	1.000	0.000	10	1	0

SEM, standard error of mean

Table 4b Summary survival table (see Table 4a)

	Observed (*n*)	Events (*n*)	Censored		Missing (*n*)	Invalid (*n*)
			(*n*)	(%)		
0	11	10	1	9.091	0	0
1	19	16	3	15.789	0	0
Total	30	26	4	13.333	0	0

Censor variable, DVM; grouping variable, IK80

study [12], 9.5 months for the NCCTG study 7, 9.5 months for the BTSG series 21, 11.5 months for one series reported by Levin et al. [14], 12.7 months for another series in which Levin tested concurrent radiotherapy and chemotherapy association [15], and 12.5 months for the Brandes study, also testing a concurrent combination [5]. The last study is a surgical series in which no patients underwent a stereotactic biopsy [5]. Our results are in accordance with these results and are similar to the best seen in the literature, and MST closer to 12.5 months [8].

Despite the low efficacity of combination therapies, when treating malignant glioma patients, the quality of life must remain the principal goal for clinicians. In our series, the hematological toxicity (grade 3 or 4 neutropenia; white blood cell count < 1500/ml) was sufficiently mild and transient so as not to result in a delay of therapy or to require parenteral support (i.e., platelet transfusion or antibiotic treatment of neutropenic fever). No grade 3 or 4 thrombopenia was noted in our study. Our hematological toxicity was comparable to that obtained in other series testing etoposide as a single drug [6, 9]. Moreover, the hematological toxicity of etoposide is known to be milder and more transient than other drugs such as nitrosoureas.

In conclusion, our present study suggests that etoposide may be used as a single agent for the treatment of newly malignant gliomas in near-concurrent combination with radiotherapy. The rate of objective response and the MST are comparable to the best results seen in the literature. The tolerance of this regimen is excellent. However, these results warrant further clinical studies to further confirm the role of etoposide as a single agent in the treatment of newly malignant gliomas.

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