Pergamon

European Journal of Cancer Vol. 32A, No. 13, pp. 2229–2235, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00299-7

Original Paper

Treatment of Recurrent Malignant Supratentorial Gliomas with Ifosfamide, Carboplatin and Etoposide: a Phase II Study

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Thirty-six patients previously treated with surgery, radiation therapy and chemotherapy with a nitrosourea for malignant supratentorial gliomas received a combination of ifosfamide, carboplatin and etoposide (ICE) at tumour progression. Carboplatin and etoposide were both given at a dose of 75–100 mg/m^2/day for 3 days, whereas ifosfamide doses ranged from 750 mg/m^2/day to 1500 mg/m^2/day for 3 days, according to haematological tolerance. Treatment was repeated every 4 weeks. A minimum of three courses was required to evaluate the response unless the patient had rapid tumour progression. Grade III and IV haematological toxicity occurred in 15 patients (42%) and was lethal in one patient. Grade II hepatic toxicity was observed in one patient. Five complete (CR) and five partial responses (PR) were noted. 9 patients had stable disease (SD) after a minimum of three courses. CR + PR + SD was 53% (19/36). The median time to tumour progression (MTTP) was 13 weeks. Median survival (MST) was 29 weeks (44 weeks for R + S patients and 17 weeks for patients with progressing disease). This study suggests that the ICE combination is active in recurrent supratentorial malignant gliomas after failure of surgery, radiation therapy and chemotherapy, but at the cost of substantial haematological toxicity. Copyright © 1996 Elsevier Science Ltd

Key words: phase II study, ifosfamide, carboplatin, etoposide, gliomas

Eur J Cancer, Vol. 32A, No. 13, pp. 2229–2235, 1996

INTRODUCTION

PATIENTS WHO develop recurrent malignant glioma after radiation therapy and nitrosourea-based chemotherapy do exceedingly poorly. In such cases, the value of second-line chemotherapy is unclear. No benefit can be expected from using another nitosourea, so different chemotherapeutic agents must be tested.

Carboplatin is a second-generation cisplatin analogue that has shown less neurotoxicity and renal toxicity [1], and crosses the blood–brain barrier more readily than its parent compound [2]. It has demonstrated activity against malignant brain tumours *in vitro* [3] and in human studies [4–8]. Etoposide (VP16-213), a semisynthetic derivative of podophyllotoxin, has shown synergistic activity with cisplatin [12–14]. Ifosfamide is an alkylating agent. Compared to its analogue, cyclophosphamide, it has demonstrated an increased therapeutic index in a variety of solid tumours (including refractory testicular cancer) and haematological malignancies [15–17]. Its main dose-limiting toxicity, haemorrhagic cystitis, is now prevented with mesna. Ifosfamide has shown synergy with etoposide and cisplatin in preclinical models [18, 19]. Furthermore, the ifosfamide–carboplatin–etoposide (ICE) combination has demonstrated a high therapeutic index in a broad range of malignancies (including sarcomas, testicular, ovarian and breast cancer, lymphoma, small cell and non-small cell lung cancer), even after failure of previous chemotherapy [20–25], and a synergistic effect among the three drugs is suggested in these studies.

The purpose of this trial was to assess the response rate, duration of remission, overall survival and toxicity of the

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Received 15 Apr. 1996; accepted 4 Jun. 1996.

Table 1. Schedule of dose escalation. Doses were increased to the next level according to haematological tolerance (nadir leucocytes > 2500/mm^3 and platelets < 100 000/mm^3). In case of grade 3 or 4 toxicity, doses were decreased to the first level, or even lower if necessary. In the other cases, drugs were maintained at the same doses

	1st level (days 1–3)	2nd level (days 1–3)	3rd level (days 1–3)
Ifosfamide	750 mg/m^2/day	1.2 g/m^2/day	1.5 g/m^2/day
Carboplatin	75 mg/m^2/day	75 mg/m^2/day	100 mg/m^2/day
Etoposide	75 mg/m^2/day	75 mg/m^2/day	100 mg/m^2/day

ICE regimen in patients with recurrent malignant supratentorial gliomas.

PATIENTS AND METHODS

Eligibility criteria

Patients eligible for the trial had first relapse malignant supratentorial glioma previously treated with surgery, radiotherapy and first-line nitrosourea-based chemotherapy. Patients had signs of tumour progression (by clinical examination showing neurological deterioration and by evidence of tumour progression on CT). Age was more than 18 years and less than 75 years and the Karnofsky performance status index was $\geqslant 40$. Eligibility criteria also included adequate bone marrow function (WBC (white blood cell) count $>3.5 \times 10^9$/l, platelet count $>100 \times 10^9$/l and haemoglobin >10 g/dl), adequate liver function (serum bilirubin <1.5 mg/dl) and renal function (serum creatinine <1.5 mg/dl).

Statistical considerations

With a 95% power to conclude the efficacy of the treatment regimen if the true response rate was $\geqslant 30\%$ and with a type I error of 10% to conclude the efficacy of the treatment if the true response rate was $\leqslant 10\%$, the number of patients required for the first stage was 26. If $\leqslant 3$ responses were observed during the first stage ($\leqslant 12\%$), then the trial would have been terminated and the treatment regimen considered inactive. If at least 4 responses were observed during the first stage, then 7 additional patients would be added. In order to consider the treatment regimen active by the end of the second stage, the total number of responses would need to be at least 6 (18%, MinMax design [26]). Time to progression was calculated from the date treatment started to the date of the first documented progression.

Survival curves were estimated using the Kaplan–Meier technique [27].

Table 2. Patient and tumour characteristics at entry

Characteristic	*n*	(%) Range
Total number of patients	36	
Age (years)		
Median (range)	53	(26–71)
Sex		
Male	26	(72%)
Female	10	(28%)
Karnofsky index		
Median (range)	70	(40–100)
Burger's histological classification [29]		
Glioblastoma multiforme	26	(72%)
Anaplastic glioma	10	(28%)
Anaplastic astrocytoma	8	
Anaplastic oligodendroglioma	2	
Time interval since surgery (weeks)		
Median (range)	43.2	(11–424)
Prior treatment		
Surgery		
Complete resection	9	(25%)
Partial resection	16	(44%)
Biopsy	11	(31%)
Irradiation (Gy)		
Median (range)	60	(50–62)
Nitrosourea-based chemotherapy (mg/m^2)		
Median (range)	405	(150–1620)

Scheme of the trial

At the first cycle, drugs were administered intravenously at 75 mg/m^2/day for carboplatin and etoposide and 750 mg/m^2/day for ifosfamide. This combination was administered from days 1 to 3, with adequate hydration and diuresis. Courses were repeated every 4 weeks until tumour progression or intolerable toxicity. Dose escalation was allowed according to haematological tolerance (Table 1). All patients were given the lowest steroid dose necessary for neurological stability. Ondansetron was given to all patients before perfusion to prevent nausea and vomiting. Neurological status, performance status and tolerance were judged on clinical, biological and CT examinations every 4 weeks. Patients were also monitored by blood counts, serum creatinine, bilirubin, ALAT (alanine aminotransferase) and ASAT (aspartate aminotransferase) every week. The World Health Organisation (WHO) scale for toxicity was used.

Response evaluation

Macdonald and associates' criteria [28] were used to evaluate the tumour response to treatment on a CT scan with contrast enhancement. A complete response (CR) was defined as the disappearance of enhanced tumour at least 1 month apart. A partial response (PR) was a reduction of 50% or more of the largest cross-sectional area of contrast enhancement. The response was considered as stable disease (SD) in the case of neurological stabilisation for at least 3 months, without a change in corticosteroid dosage, and when the largest cross-sectional area of contrast enhancement on the CT scan did not increase more than 25%. Progression was defined as neurological degradation or increase of the largest cross-sectional area of contrast enhancement on the CT scan over 25%.

RESULTS

Between 11 October 1993 and 27 December 1994, 37 patients were registered into the trial. One patient was judged to be ineligible because of poor performance status (Karnofsky index = 30). Table 2 presents the patient and tumour characteristics for all eligible patients before starting treatment. All patients were treated by surgery and post-

Table 3. Haematological toxicity (WHO scale)

	Grade 1	Grade 2	Grade 3	Grade 4
Leucocytes	4	2	9	5
Platelets	6	3	2	4

Table 4. Response to treatment

Response	Glioblastomas multiforme	Anaplastic gliomas	All patients (%)
Complete response	2	3	5 (14)
Partial response	3	2	5 (14)
Stable disease	8	1	9 (25)
Progression	13	3	16 (44)
Early death	0	1	1 (3)

operative irradiation followed by a nitrosourea-based chemotherapy. The radiotherapy was delivered using 1.8 Gy per fraction 5 times a week on a large focal field including the tumour and adjacent parenchyma (median total dose: 60 Gy). The chemotherapy was intravenous (i.v.) BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) in 33 patients, intra-arterial (i.a.) ACNU (1-(4-amino-methyl-5-pyrimidyl)-methyl-3-(2-chloroethyl)-3-nitrosourea) in 2 patients and procarbazine–CCNU–vincristine (PCV) in 1 patient. Other details are provided in Table 2.

Tolerance

The number of courses per patient ranged from 1 to 16. 8 patients received only 1 cycle, 8 received 2 cycles, 4 received 3 cycles, 3 received 4 cycles, 4 received 5 cycles, 8 received 6 cycles or more, including 1 patient who received 16 cycles. The median number of cycle per patients was 4. 14 patients (39%) experienced no haematological toxicity, 7 patients (19%) had grade I–II, 9 (25%) had grade III and 6 (17%) had grade IV. Grade III or IV toxicity involved leucocytes in 14 patients and platelets in 6 patients (Table 3). One patient died from sepsis during an episode of leucopenia (0.9×10^9/l). No other life-threatening events were observed. Nausea and vomiting occurred in 3 patients. One patient developed hepatic toxicity grade II with increased SGPT level. None had renal, peripheral neuropathy or auditory toxicity. No haemorrhagic cystitis or encephalopathy were observed.

For the patients who had haematological toxicity, the doses were kept at the first level (see Table 1). However, for 3 patients, the dose had to be further reduced by 10–25%. Among the 28 patients who received more than 1 course, tolerance allowed a dose increase to the second level in 15 patients, but the third level could only be administered to 2 patients.

Therapeutic effects

Table 4 presents the response to treatment by histological subtype. The overall response rate (CR + PR) was 10/36 (28%, 95% confidence limits: 14–45%). Together with patients with stable disease, this percentage was 53% (95% confidence limits: 36–70%). For the 10 patients who

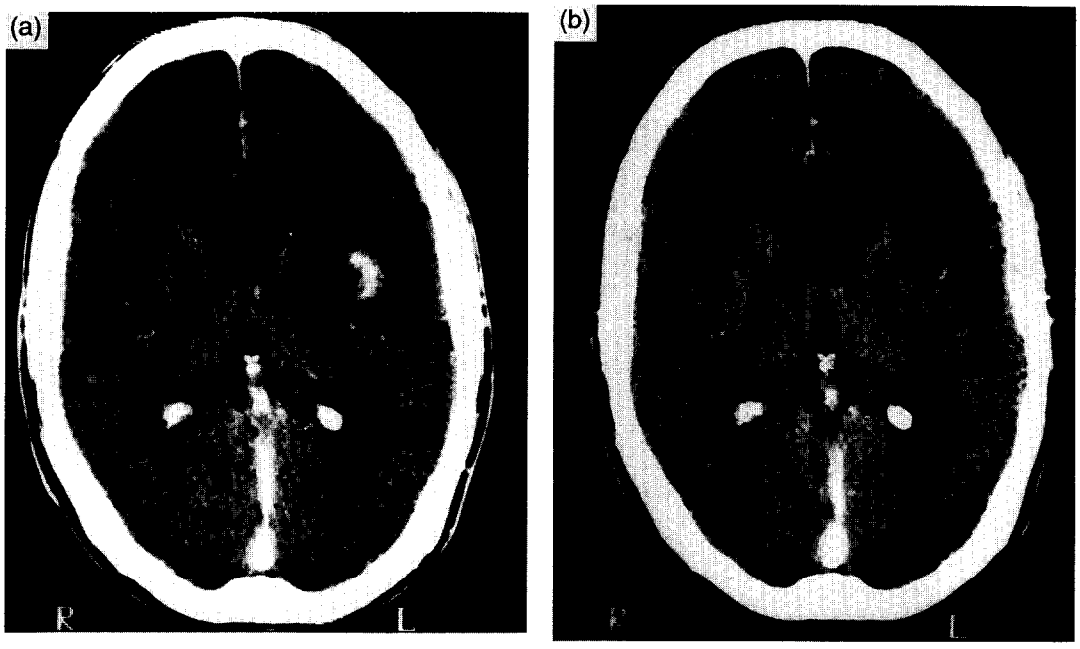

Figure 1. (a) CT scan of a patient with an anaplastic glioma at recurrence; (b) CT scan after one cycle of ICE. The complete response was maintained for 82 weeks.

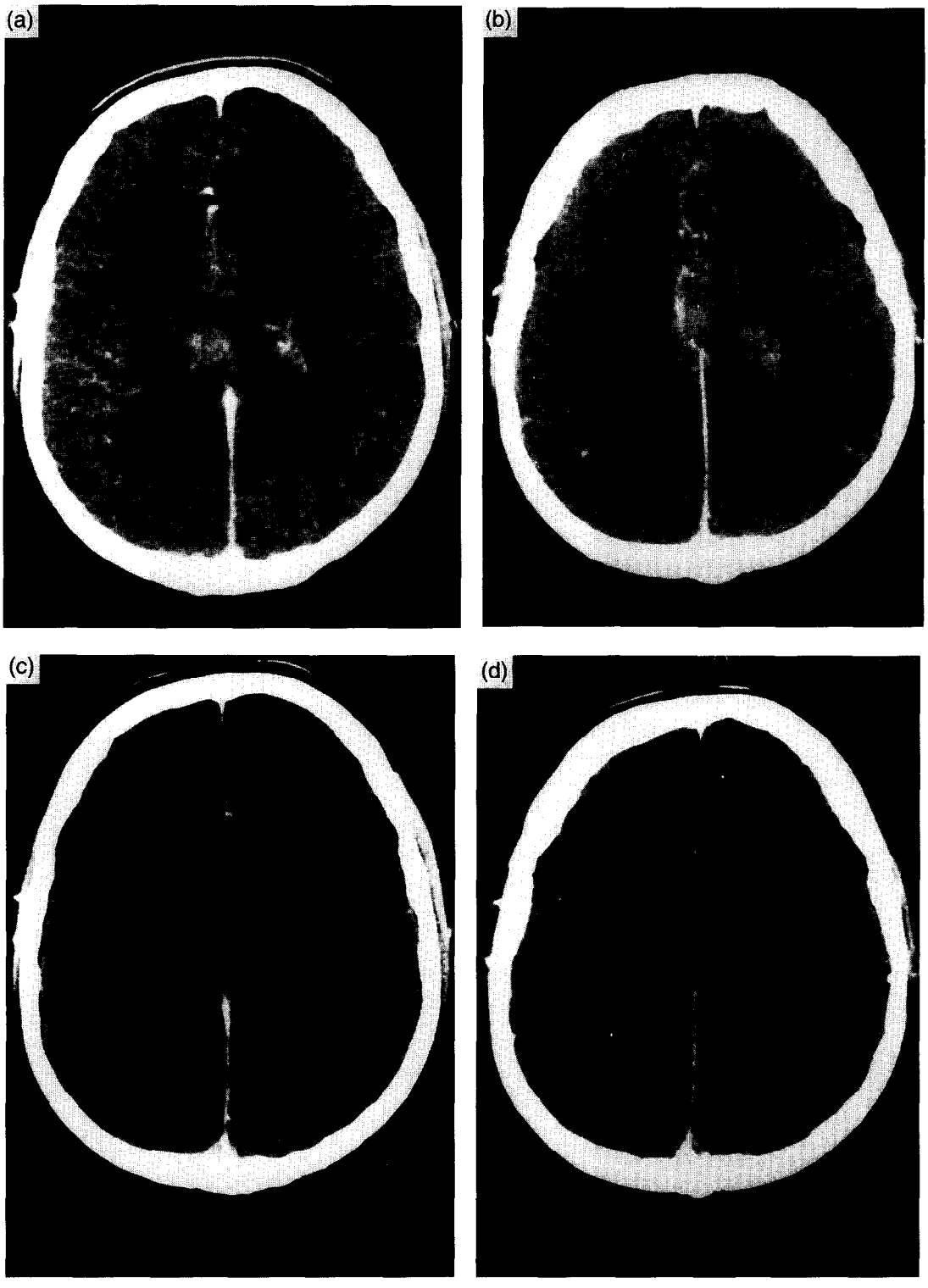

Figure 2. (a) and (b) CT scan of a patient with an anaplastic glioma at recurrence; (c) and (d) a partial response was observed after 3 months and was maximum after 6 months.

responded, the objective response on CT was noted after 1 cycle in 5 patients, 2 cycles in 3 patients and 3 cycles in 2 patients. The maximum effect was observed as late as 6 months after starting the treatment. Among complete responders, the response lasted for 8 and 22 weeks for the glioblastoma multiforme patients and for 8, 22 and 82 weeks for the anaplastic glioma patients (Figure 1). For the 5 patients with partial response, the duration of response was 14, 25 and 31 weeks for the glioblastoma multiforme patients and 28 and 35 for the anaplastic glioma patients (Figure 2).

Based on all eligible patients, the median time to progression was 13 weeks and 22 weeks for stable and responding patients (Table 5 and Figure 3). At the time of analysis,

Table 5. Median time to tumour progression (MTTP) and median survival time (MS) calculated for stable or responding (R + S) patients and for patients with progressive disease (PD) (weeks)

	R + S		PD		Total	
	MTTP	MS	MTTP	MS	MTTP	MS
Glioblastomas	21	40	6	20	12.5	29
Anaplastic gliomas	25	61	5	11	14	25
Total	22	44	5	17	13	29

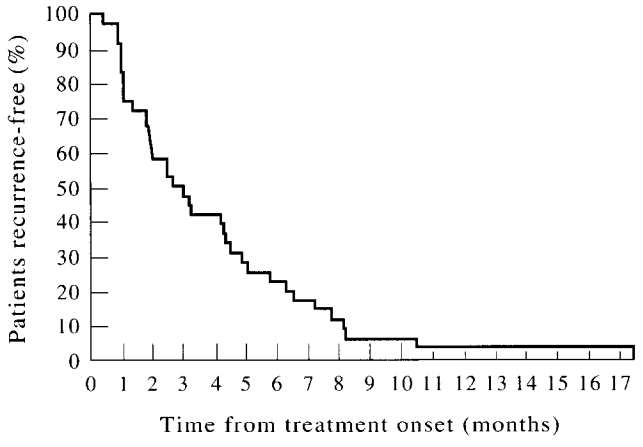

Figure 3. Time to tumour progression for all patients.

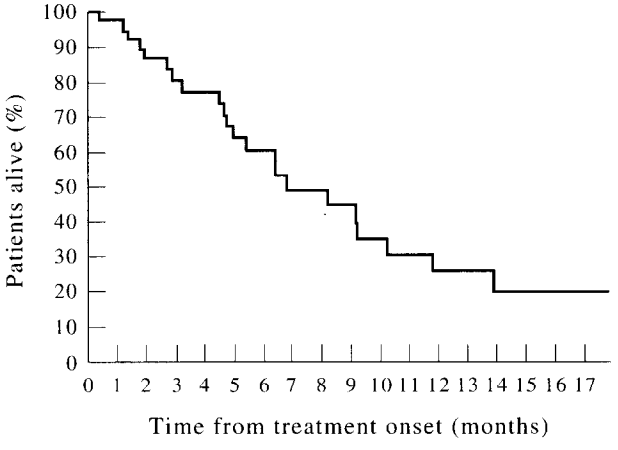

Figure 4. Survival curve for all patients.

23 patients had died and the median duration of survival was 29 weeks (44 weeks for R + S patients and 17 weeks for patients with progressing disease) (Table 5 and Figure 4). The median duration of survival from the initial surgery was 67 weeks.

DISCUSSION

This study suggests that the combination of ICE for recurrent malignant glioma is of therapeutic benefit as second-line chemotherapy at the price of substantial haematological toxicity. Indeed, nine grade 3 (25%) and six grade 4 (17%) haematological toxicities were observed and 1 patient died of a septic shock related to grade 4 neutropenia. Haematological toxicity was, therefore, more frequent and serious than with the carboplatin–etoposide combination; 19% grade 3 and no grade 4 toxicity were observed with this combination (at a dose of 100 mg/m^2/day on days 1 to 3 for both drugs) [14].

The prognosis of recurrent malignant glioma after conventional radiotherapy and first-line chemotherapy is so poor that many patients are not offered a second-line chemotherapy regimen. Nevertheless, in this study, we found clear evidence that some patients may benefit from ICE combination since the response rate (R) was 28% and the rate of response plus stabilisation (R + S) was 53%.

These results concur with recent reports suggesting that carboplatin or carboplatin-based chemotherapy could be of interest as second-line treatment. When used alone in recurrent malignant gliomas, carboplatin induces a response rate (R) of 10–14% and a (R + S) rate of 40–50% [4–8, 30]. The carboplatin–etoposide combination appeared synergistic *in vitro* [11], and may be considered an efficient second-line chemotherapy: response rate and R + S rate ranged, respectively, from 13% to 21% and from 45% to 53% [13, 14].

In contrast, treatment of recurrent malignant gliomas with ifosfamide alone demonstrates poor efficiency despite the high doses used. Of 42 patients with recurrent malignant glioma reported in the literature [31–34], 2 had a partial response and 5 stable disease (S + R = 17%) (Table 6). However, there is evidence that the ifosfamide–etoposide combination could be synergistic [35]. This association displayed some efficacy in paediatric recurrent gliomas since Miser and associates observed one PR and 7 SDs out of 16 supratentorial recurrent malignant gliomas in children [36].

Compared to the other chemotherapy regimens (see Table 7), the ICE combination appears as one of the most interesting second-line treatments of recurrent malignant gliomas. In our experience, it seems more efficient than the carboplatin–etoposide combination administered at the dose of 100 mg/m^2/day on days 1–3 of each drug [14]. Nevertheless, Jeremic and associates observed a comparable R + S rate (53%) and higher MST (43.5 weeks) using high doses of carboplatin (300 mg/m^2/day on days 1–3) and etoposide (100 mg/m^2/day on days 1–5) at the price of substantial grade 3 blood toxicity (55%) [13]. Procarbazine also has demonstrated activity against malignant gliomas after failure of nitrosourea: the R + S rate ranged from 35% to 57% [37, 38, 42]. Differences in prognostic factors (age, Karnofsky index and grading) are very important and, in addition to lack of randomisation, make comparison between phase II studies difficult. Yet prognostic factors of our patients were fairly representative of a non-biased cohort of recurrent gliomas, and ICE demonstrates a strong antitumoral effect even in glioblastoma, the most malignant and chemoresistant of these tumours. With 19% (5/26) response (R) rate, 50% (13/26) (R + S) rate, and a 29-week median survival time in the glioblastoma population, our results are close to those observed by Levin and associates (58% of

Table 6. Ifosfamide-based protocols in malignant gliomas

[Ref.]	Drugs	Patients	CR	PR	SD	R + S
[31]	Ifos	16	0	0	1	1/16
[32]	Ifos	4	0	0	0	0/4
[33]	Ifos	6	0	1	3	4/6
[34]	Ifos	16	0	1	1	2/16
Total	(Ifos alone)	42	0	2	5	7/42 (17%)
[36]	Ifos/VP 16	16	0	1	7	8/16 (50%)

CR, complete response; PR, partial response; SD, stable disease; R + S, responding and stable patients.

Table 7. Phase II studies of second-line chemotherapy in recurrent malignant gliomas

[Ref.]	Patients	Chemotherapy	R + S (%)	R (%)	MST
[36]	16	Ifos–VP16	50	7	—
[37]	37 GBM	Procarbazine	27	13.5	—
	46 AA		28	14	—
[5]	19	Carbo (i.a.)	52	26	—
[38]	35	Procarbazine	57	14	—
[39]	16 (1)*	Endoxan–VCR	75	31	—
[31]	16	Ifos	6	0	20
[7]	19	Carbo	40	10	26
[40]	32 (11)*	Acivicine	34	12	—
[6]	15	Carbo or Iproplatin	13	13	—
[13]	38	Carbo–VP16	53	21	43.5
[41]	19 GBM	TPDC–FUHU**	58	16	—
	13 AA		38	15	—
[14]	31	Carbo–VP16	45	13	—
[42]	20	Procarbazine–Thiotepa–VCR	25	15	17
[43]	31	Procarbazine	55	35.5	—
[30]	28	Carbo	50	7	36
[24]	16	Ifos	12.5	6	—
Present study	36	Ifos–Carbo–VP16	54	29	29

* The numbers in parentheses indicate the number of patients treated as first-line chemotherapy. ** TDPC-FUHU, CCNU-thioguanine-dibromodulcitol-procarbazine + fluorouracil-hydroxyurea. i.a., intra-arterial; VP16, etoposide; Carbo, carboplatin; VCR, vincristine; Ifos, ifosfamide; R, responding patients; R + S, responding and stable patients; MST, median survival time.

R + S), who developed a polydrug protocol designed to combat nitrosourea resistance [41].

In conclusion, the ICE regimen has shown at least comparable results to the most widely used second-line chemotherapy regimen in recurrent malignant gliomas, such as procarbazine or carboplatin–etoposide. These results warrant further studies to confirm these data and to optimise treatment which is limited by haematological toxicity and particularly leucopenia. This could be prevented by systematic use of G-CSF and/or sequential reinfusion of progenitors of whole blood, which have already been undertaken with success in the treatment of several malignancies [21, 22].

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