Pergamon

European Journal of Cancer, Vol. 34, No. 10, pp. 1570–1574, 1998
© 1998 Elsevier Science Ltd. All rights reserved
Printed in Great Britain
0959-8049/98/$—see front matter

PII: S0959-8049(98)00138-5

Original Paper

Phase II Study on Cisplatin and Ifosfamide in Recurrent High Grade Gliomas

M.J. van den Bent,[1] J.H.M. Schellens,[2] Ch.J. Vecht,[1] P.A.E. Sillevis Smit,[1] O.J.L. Loosveld,[2] J. Ma,[2] C.C. Tijssen,[3] R.L.H. Jansen,[4] J.M. Kros[5] and J. Verweij[2]

[1]Department of Neuro-Oncology, Rotterdam Cancer Institute; [2]Department of Medical Oncology, Rotterdam Cancer Institute and University Hospital, Rotterdam; [3]Department of Neurology, St Elisabeth Gasthuis, Tilburg; [4]Department of Internal Medicine, University Hospital, Maastricht; and [5]Department of Pathology, Rotterdam University Hospital, Rotterdam, The Netherlands

27 patients with recurrent high grade glioma following surgery and radiation therapy were treated with 100 mg/m^2 cisplatin and 6 g/m^2 ifosfamide per cycle, administered on days 1–3 in 4 week cycles, for a maximum of six cycles. Toxicity was assessed after every cycle. Response was assessed following every second cycle, and a 50% decrease of the largest cross-sectional tumour area on contrast enhanced magnetic resonance imaging or computed tomography scan was considered a partial response (PR). A total of 95 cycles was administered; 26 patients were evaluable for response. In 5 patients (19%), a PR was obtained (median time to progression (TTP): 34 weeks). Stable disease was observed in 6 patients (23%, median TTP: 22 weeks). The most frequent toxicity was haematological: 37% of cycles were complicated by a grade 3 or 4 leucopenia. 1 patient died, probably as a consequence of increased cerebral oedema induced by the cisplatin hydration schedule. Determination of the cisplatin concentration in this patient showed a 10-fold increase in the tumour concentration as compared with that in normal brain tissue, demonstrating the absence of a blood–brain barrier in the tumour. In conclusion, generally this schedule was well tolerated, but it is of moderate activity for recurrent glioma. **© 1998 Elsevier Science Ltd. All rights reserved.**

Key words: chemotherapy, cisplatin, glioma, ifosfamide, oligoastrocytoma, recurrent
Eur J Cancer, Vol. 34, No. 10, pp. 1570–1574, 1998

INTRODUCTION

THE OUTCOME of treatment for anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) remains dismal. The median survival time following surgery and radiation therapy is less than 1 year. Although adjuvant chemotherapy is of some benefit, it only improves the median survival by 2–3 months [1]. Treatment possibilities for recurrent glioma are limited. Patients with a good performance status, a long progression-free interval and in whom a significant second resection can be performed may benefit from re-operation [2, 3]. Re-irradiation is usually not possible, due to neurological side-effects. Thus, in many patients, chemotherapy is the only remaining treatment option. Unfortunately, studies on chemotherapy for recurrent high grade glioma show only modest response rates, with limited duration of the observed responses. This calls for further trials to develop more active treatment schedules. We decided to combine cisplatin and ifosfamide, as in experimental models therapeutic synergism of this combination was observed, and high response rates have been observed in melanoma, ovarian cancer and non-small cell lung cancer [4–8]. Thus, we investigated in a multicentre phase II trial a dose-intensive regimen containing cisplatin 100 mg/m^2 and ifosfamide 6 g/m^2 in 4 weekly cycles in chemonaïve patients with recurrent high grade glioma. The study was carried out with ethical committee approval.

PATIENTS AND METHODS

Patients were eligible if they had a histologically proven high grade glioma or recurrence more than 4 weeks after completion of radiation therapy, documented on magnetic

Correspondence to MJ. van den Bent.
Received 16 Oct. 1997; revised 9 Feb. 1998; accepted 24 Mar. 1998.

resonance imaging (MRI) or computed tomography (CT) scan; had not received prior chemotherapy; had a WHO performance status of 0–2; had measurable disease on CT or MRI scan and adequate bone marrow (platelets $> 100 \times 10^9$/l, white blood count $> 3.0 \times 10^9$/l), renal (serum creatinin < 120 μmol/l or creatinine clearance > 60 ml/min) and liver function (bilirubin < 25 μmol/l, and serum albumin > 30 g/l), with no cardiac disease precluding adequate hydration; and had provided informed consent according to institutional rules. If patients underwent a second operation, measurable disease required either a CT or MRI scan within 3 days of surgery, measurable disease outside the operation area (e.g. the contralateral hemisphere), or documented progression following surgery.

Treatment schedule

Ifosfamide 2 g/m^2 was administered daily on days 1–3 as a 4 h infusion combined with mesna 400 mg/m^2 intravenously by bolus administration three times daily. This was followed by cisplatin 33.3 mg/m^2 administered daily on days 1–3 as a 3 h infusion in hypertonic saline (3%). On each treatment day, prehydration and posthydration were given. Prehydration consisted of 0.75 l dextrose saline in 3 h combined with 20 mmol KCl and 2 g $MgSO_4$; posthydration consisted of 2 l dextrose saline in 14 h combined with 40 mmol KCl and 4 g $MgSO_4$. On each day of treatment, patients were given antiemetics including 10 mg dexamethasone and a $5HT_3$-antagonist. During the remainder of the 4-week period, dexamethasone was prescribed as indicated. Cycles were repeated every 4 weeks, up to a maximum of six cycles in responding or stabilised patients. In case of progressive disease, treatment was stopped.

Evaluation of response

The response to treatment was evaluated following every second cycle by clinical evaluation and preferentially MRI scan; CT scan was used if MRI scanning was not possible. For an individual patient, the same imaging modality was used throughout the entire study period. A baseline scan was obtained within the 2 weeks before the start of treatment. For evaluation, the slice with the largest tumour area was used. Tumour size was defined as the product of the two largest perpendicular tumour diameters. A complete response (CR) was defined as the disappearance of all tumour on two consecutive scans at least 4 weeks apart, the patient being off steroids and neurologically stable or improved. A partial response (PR) was defined as a 50% or greater reduction in cross-sectional tumour area on scans at least 1 month apart, steroids stable or decreased and neurologically stable or improved. Progressive disease (PD) was defined as a 25% or greater increase in cross-sectional tumour area, a new tumour on CT or MRI or neurological deterioration and steroids stable or increased. All other situations were considered stable disease (SD). The time to tumour progression was measured from the start of chemotherapy to the first sign of radiological or clinical progression.

Evaluation of toxicity

Patients had weekly assessment of haemoglobin, leucocytes and platelets. Before the start of every cycle, renal and liver function were assessed. For evaluation of toxicity, the NCI Common Toxicity Criteria (CTC) were used, and toxicity was measured during each cycle.

Determination of cisplatin concentration

An autopsy was performed on a patient who died immediately after the first administration of cisplatin. Following 1 month of fixation in formaldehyde, the brain was cut into slices of 1–1.5 cm thick. These slices were cut into 1×1 cm cubes; large vessels and other non-brain material were removed. These cubes were subsequently frozen (-70°C). After thawing, rows of these cubes passing through and above the tumour were examined for cisplatin concentration and tumour cells. Each cube was divided in half. One half was used for histological examination for the presence of tumour, necrosis and oedema. The other half was used for the measurement of cisplatin concentration, which was determined by frameless atomic absorption as described elsewhere [9]. The platinum concentration was expressed as pg platinum per mg tissue.

RESULTS

27 patients were entered into the study and their characteristics are described in Table 1. 1 patient with a WHO score of 3 due to a fixed hemiplegia for more than 1 year following earlier surgery was also accepted for inclusion. Of the 6 patients initially with an astrocytoma grade II (AII), 2 were re-operated upon at which time they were diagnosed with a grade IV oligoastrocytoma. The other 4 had clearly enhancing recurrences on MRI scan, suggestive of a high grade tumour. The patient with a low grade oligoastrocytoma also developed a histologically proven grade IV oligoastrocytoma. Eleven years before, 1 patient had been treated for a meningeal fibrosarcoma by surgery and involved field radiation therapy (62.4 Gy). She then developed a GBM in the radiated field, which was treated with gross total resection only. After diagnosis of tumour progression, chemotherapy was started.

1 patient with a GBM was included following clinical deterioration 3 months after the end of radiation therapy, with MRI showing a slight increase of the enhancing area. He then received five cycles of chemotherapy, which were complicated by repeated episodes of seizures and headache. Following the fifth cycle, there seemed to be some increase in the tumour and chemotherapy was discontinued. Nine months later he was still doing well, and MRI showed more than a

Table 1. *Patient characteristics (number of patients entered:* 27*)*

Male:female	14:13
Age (years)	
Median	42
Range	20–62
ECOG	
0	7
1	14
2	5
3	1
Tumour histology at first surgery	
Glioblastoma multiforme	12
Anaplastic astrocytoma	7
Low grade astrocytoma	6
Anaplastic oligodendroglioma	1
Low grade oligoastrocytoma	1
Former treatment	
Surgery only	1
Surgery and radiation therapy	16
Surgery, radiation therapy and second surgery	10

50% reduction in the tumour area. As this clinical course casts doubt on both the cause of deterioration and the subsequent improvement, he is precluded from the response analysis but was included in survival analysis. A total of 95 cycles were administered (median 3 cycles, range 1–6), 6 patients received the intended six cycles.

Response

All but 2 patients had died at the time of analysis. No CRs were seen. 5 patients (2 GBM, 1 AA, 2 AII) achieved a PR (19%), with a median time to progression (TTP) of 34 weeks (range: 18–44+ weeks). 6 patients (4 GBM, 2 AII) had SD, with a median TTP of 22 weeks (range 18–28 weeks); the other 15 patients had PD. In 2 patients, the first evaluation scan showed a 50% reduction, but at the next evaluation of response, progression was diagnosed—they were classified as SD. In another 2 patients, a 25% decrease of tumour area was noted.

The median TTP for all patients was 14 weeks (Table 2), for those with a PR or SD it was 26 weeks. 6 patients (23%) remained free from progression for more than 6 months. The median survival time (MST) for all patients was 25 weeks, for patients with a PR or SD it was 43 weeks. In univariate analysis, no relationship was found between the response rate and tumour histology, age, performance state or initial disease-free survival. None of the 4 patients with an oligodendroglial tumour responded to treatment.

Toxicity

1 patient with a large temporal recurrent glioblastoma with brain stem compression deteriorated immediately following the end of the first cycle. A control CT scan showed an increase of oedema, and he died 1 day later. In a second patient, the first cycle was interrupted because of stupor. He recovered completely and treatment was continued. 25 patients were, therefore, evaluable for other toxicities. The most frequent toxicity was haematological (Table 3). Twenty-two cycles (23%) were complicated by grade 3 and 13 cycles (14%) by grade 4 leucopenia. 1 patient suffered twice from a sepsis during leucopenia, but recovered uneventfully. In addition, there were three more episodes of neutropenic fever. Grade 3 nausea or grade 3/4 vomiting was observed in six cycles. No renal toxicity was seen. In 1 patient, treatment was discontinued after three cycles because of coinciding ototoxicity and progressive disease. In 6 patients, dose reductions were necessary, all for haematological toxicity. 1 responding patient suffered from a non-treatment-related pulmonary embolus.

Table 2. Median time to progression (TTP) and median survival time (MST) in weeks for all patients and for those with either a partial response (PR) or stable disease (SD), subdivided for histology at the time of first surgery (glioblastoma multiforme (GBM) or other)

Histology at first surgery	All patients			PR+SD		
	n	TTP	MST	*n*	TTP	MST
GBM	12	13	31	6	27	39
Others	15	8	21	5	25	44
Total	27	14	25	11	26	43

Table 3. Grade 3 or 4 haematological toxicity

	Grade 3 No. of cycles (No. of patients)	Grade 4 No. of cycles (No. of patients)
Leucopenia	22 (9)	13 (7)
Thrombopenia	3 (2)	4 (2)
Anaemia	2 (2)	2 (1)

Pharmacokinetic study

Histological examination of the patient who died immediately after the first cycle showed a relatively sharp transition from tumour to surrounding brain. Samples from areas around the tumour only showed necrosis and oedema, without infiltrating tumour cells. The cisplatin concentration in the tumour was 10-fold higher than in the contralateral hemisphere (Table 4). At a distance of > 3 cm from the tumour, the cisplatin concentration was comparable with the concentration in the contralateral hemisphere, despite the presence of significant oedema. In this single patient, no relationship was present between the amount of oedema or necrosis and the platinum concentration.

DISCUSSION

Single agent studies on intravenous cisplatin and ifosfamide in recurrent high grade glioma are scarce, and difficult to compare due to large differences in response criteria. Also, many of the patients in these studies were heavily pretreated, including adjuvant or salvage chemotherapy, in particular with nitrosoureas. Studies on cisplatin showed only modest activity, with responses of short duration [10–12]. A dose intensified study in which 100 mg/mg^2 cisplatin was given on day 1 and day 8 in 4 week cycles reported 27% objective response with a median TTP of only 8 weeks [10–12]. Single agent studies on the platinum analogue carboplatin also showed limited objective response rates: up to 10% with a median TTP of 5–6 months [13–15]. One trial on single agent chemotherapy with ifosfamide reported no responses, but in paediatric studies conflicting results were reported [16–18]. Studies on combinations of a platinum derivative and etoposide reported response rates of 13–21% and a median TTP of 6–10 months [19–21]. Interestingly, of 36 patients, 28% responded to a combination of ifosfamide, carboplatin and etoposide (ICE), with a median TTP of 24 weeks. In that study, 53% of patients either responded or stabilised, and among the responders were 5 CRs [22].

Table 4. Platinum concentration in the brain of 1 patient

	pg platinum per mg tissue
Contralateral hemisphere	
White matter	33–40
Grey cortical zone	76–130
Ipsilateral hemisphere	
Tumour	300–500
1 cm zone immediately around the tumour	100–280
Zone 2–3 cm away from the tumour	50–100
> 3 cm away from the tumour, in area with oedema	
White matter	30–45
Grey cortical zone	60–110

The present study was performed in a similar group of patients, except for one major difference: all our patients were chemonaïve. With this combination of cisplatin and ifosfamide, we observed a 19% (5/26) response rate (median TTP 34 weeks), with 23% (6/26) SD (median TTP 22 weeks). Although this response rate is less favourable than observed in the above-mentioned ICE study, 23% of our patients were free from progression at 6 months as seen in that study [20]. Both studies are also comparable with regard to median TTP and MST, for both the whole group and the responding or stabilised patients. These studies suggest that the addition of ifosfamide to cisplatin with or without etoposide may increase the response rate of recurrent gliomas. The results of these cisplatin-based studies are comparable to the results of nitrosourea based chemotherapy in recurrent glioma [23]. Our study also emphasises the importance of strict and uniform response criteria for brain tumour studies: if a short-lasting 50% decrease or an enduring 25% decrease was also considered as a PR, as previously done in other studies [10, 14], the response rate would almost double to 36% with a median TTP of 6 months.

In general, treatment was well tolerated, despite the frequent haematological toxicity. Thirty-seven per cent of cycles were complicated by a grade 3 or 4 leucopenia, from which all patients recovered. 2 patients developed acute neurological deterioration during the first cycle, which was fatal in 1 patient. This is a known complication of cisplatin chemotherapy for brain tumours [24]. It is due to increased brain oedema following the hydration schedule, which is necessary to avoid the nephrotoxicity of cisplatin. We presently administer an additional dexamethasone bolus of 10–20 mg the day before each cycle in patients with large tumours with significant oedema, or with a midline shift, to prevent an increase of oedema. One reason for the relative resistance of gliomas to chemotherapy might be the blood–brain barrier. In the autopsied patient, the simultaneous microscopic and histological examination allowed a precise determination of the cisplatin concentration in relation to the tumour, brain around the tumour and normal brain. Our findings confirm the presence of a disturbed blood–brain barrier in brain tumours. The cisplatin concentration in the tumour was 10-fold higher than in the white matter of the contralateral hemisphere. Even in the brain around the tumour area with possible microscopic infiltration, a high cisplatin concentration was present. These findings are in agreement with both experimental and clinical work of others, suggesting that the limited antitumour activity of cisplatin in glioma is due to an intrinsic resistance to cisplatin of these tumours [25–27]. Although this questions the role of blood–brain barrier modification or intracarotid administration as advocated by others, it may still be that an increased cisplatin penetration increases the response of the tumour due to local dose intensification [27–29]. In conclusion, this schedule of combined cisplatin and ifosfamide showed modest activity in recurrent glioma, and was in general well tolerated despite the observed haematological toxicity. However, the modest results of this and other comparable studies question whether the percentage of patients responding or stabilised for a relatively limited period of time outweigh this intensive treatment and follow-up.

1. Fine HA, Dear KBG, Loeffler JS, Black PMcL, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993, **71**, 2585–2597.
2. Ammirati M, Galicich JH, Arbit E, Liao Y. Reoperation in the treatment of recurrent intracranial malignant gliomas. *Neurosurg* 1987, **21**, 607–614.
3. Vick NA, Ciric IS, Eller TW, Cozzens JW, Walsh A. Reoperation for malignant astrocytoma. *Neurology* 1989, **39**, 430–432.
4. Goldin A. Ifosfamide in experimental tumor systems. *Semin Oncol* 1982, **9**, 14–23.
5. Graziano S, Herndon JE, Richards F, *et al.* A phase I trial of ifosfamide, mesna and cisplatin in advanced non-small cell lung cancer. *Cancer* 1993, **72**, 62–68.
6. Green JA, Slater ALJ. A study of cisplatinum and ifosfamide in alkylating agent-resistant ovarian cancer. *Gynecol Oncol* 1989, **32**, 233–235.
7. Becher R, Seeber S, Schmidt CG. Combination chemotherapy with ifosfamide and cis-dichlorodiammineplatinum (II) in advanced malignant melanoma. *J Cancer Res Clin Oncol* 1980, **97**, 301–306.
8. Verweij J, Planting AST, Gaast A van de, Stoter G. Phase II study of cisplatin plus 24-hour infusion of ifosfamide in advanced malignant melanoma. *Ann Oncol* 1990, **1**, 77–78.
9. Ma J, Verweij J, Kolker HJ, Ingen HE van, Stoter G, Schellens JHM. Pharmacokinetic–dynamic relationship of cisplatin in vitro simulation of an iv bolus, 3h and 20h infusion. *Br J Cancer* 1994, **69**, 858–862.
10. Spence AM, Berger MS, Livingston RB, Ali-Osman F, Griffin B. Phase II evaluation of high-dose intravenous cisplatin for the treatment of adult malignant gliomas recurrent after chloroethylnitrosurea failure. *J Neurooncol* 1992, **12**, 187–191.
11. Stewart DJ, O'Bryan RM, Al-Sarraf M, Costanzi JJ, Oishi N. Phase II study of cisplatin in recurrent astrocytomas in adults: a southwest oncology group study. *J Neurooncol* 1983, **1**, 145–147.
12. Grunberg SM, Bertram JH, MeDermed JE, Apuzzo MLJ. Treatment of astrocytoma with a 5-day cisplatin infusion. *Cancer Drug Delivery* 1987, **4**, 47–53.
13. Warnick RE, Prados MD, Mack EE, *et al.* A phase II study of intravenous carboplatin for the treatment of recurrent gliomas. *J Neurooncol* 1994, **19**, 69–74.
14. Poisson M, Pereon Y, Chiras J, Delattre JY. Treatment of recurrent malignant supratentorial gliomas with carboplatin (CBDCA). *J Neurooncol* 1991, **10**, 139–144.
15. Yung WKA, Mechtler L, Gleason MJ. Intravenous carboplatin for recurrent malignant glioma: a phase II study. *J Clin Oncol* 1991, **9**, 860–864.
16. Elliott TE, Buckner JC, Cascino TL, Levitt R, O'Fallon JR, Scheithauer BW. Phase II study of ifosfamide with mesna in adult patients with recurrent diffuse astrocytoma. *J Neurooncol* 1991, **10**, 27–30.
17. Pratt CB, Douglass EC, Kovnar EH, *et al.* A phase I study of ifosfamide given on alternative days to treat children with brain tumors. *Cancer* 1993, **71**, 3666–3669.
18. Heideman RL, Douglass EC, Langston JA, *et al.* A phase II study of every other day high-dose ifosfamide in pediatric brain tumors: a Pediatric Oncology Group Study. *J Neurooncol* 1995, **25**, 77–84.
19. Jeremic B, Grujicic D, Jevremovic S, *et al.* Carboplatin and etoposide chemotherapy regimen for recurrent malignant glioma: a phase II study. *J Clin Oncol* 1992, **10**, 1074–1077.
20. Buckner LC, Brown LD, Cascino TL, *et al.* Phase II evaluation of infusional etoposide and cisplatin in patients with recurrent astrocytoma. *J Neurooncol* 1990, **9**, 249–254.
21. Ameri A, Poisson M, Chauveinc L, Chen QM, Delattre JY. Treatment of recurrent malignant supratentorial gliomas with the association of carboplatin and etoposide: a phase II study. *J Neurooncol* 1997, **32**, 155–160.
22. Sanson M, Ameri A, Monjour A, *et al.* Treatment of recurrent malignant supratentorial gliomas with ifosfamide, carboplatin and etoposide: a phase II study. *Eur J Cancer* 1996, **32A**, 2229–2235.
23. Rajan B, Ross G, Lim CC, *et al.* Survival in patients with recurrent glioma as a measure of treatment efficacy: prognostic factors following nitrosurea chemotherapy. *Eur J Cancer* 1994, **30A**, 1809–1815.
24. Walker RW, Cairncross JG, Posner JB. Cerebal herniation in patients receiving cisplatin. *J Neurooncol* 1988, **6**, 61–65.

25. Ichimura K, Ohno K, Aoyagi M, Tamaki M, Suzuki R, Hirakawa K. Capillary permeability in experimental rat glioma and effects of intracarotid CDDP administration on tumor drug delivery. *J Neurooncol* 1993, **1993**, 211–215.
26. Stewart DJ, Leavens M, Maor M, *et al.* Human central nervous system distribution of cis-diamminedichloroplatinum and use as a radiosensitizer in malignant brain tumors. *Cancer Res* 1982, **42**, 2474–2479.
27. Stewart DJ, Mikhael NZ, Nair RC, *et al.* Platinum concentrations in human autopsy tumor samples. *Am J Clin Oncol* (CCT) 1988, **11**, 152–158.
28. Stewart DJ, Molepo MJ, Eapen L, *et al.* Cisplatin and radiation in the treatment of tumors of the central nervous system: pharmacological considerations and results of early studies. *Int J Radiat Oncol Biol Phys* 1993, **28**, 531–542.
29. Nakagawa H, Fujita T, Izumoto S, *et al.* Cis-diamminedichloroplatinum (CDDP) therapy for brain metastasis of lung cancer. *J Neurooncol* 1993, **16**, 61–67.

Acknowledgement—This study was supported in part by a grant from ASTA Medica AG, Frankfurt/Germany.