PERGAMON

European Journal of Cancer 36 (2000) 1026–1031

European Journal of Cancer

www.ejconline.com

Up-front chemotherapy with fotemustine (F)/cisplatin (CDDP)/ etoposide (VP16) regimen in the treatment of 33 non-removable glioblastomas

M. Frenay [a], C. Lebrun [b,*], M. Lonjon [c], P.Y. Bondiau [a], M. Chatel [b]

[a] *Centre de Lutte Contre Le Cancer 'Antoine Lacassagne', 06100 Nice, France*
[b] *Service de Neurologie, Pavillon D Hôpital Pasteur, 30 voie Romaine, BP69, F-06002 Nice Cedex 1, France*
[c] *Service de Neurochirurgie, Hôpital Pasteur, 06100 Nice, France*

Received 1 September 1999; received in revised form 23 December 1999; accepted 9 February 2000

Abstract

Despite combinations of surgery, radiotherapy (RT) and chemotherapy used in the treatment of glioblastomas, mean and median survival rates in most patients remain 12 months or less after diagnosis. RT and nitrosourea after surgery are the standard combination for glioblastomas. They may induce acquired resistance and, consequently, non-operable glioblastomas is a unique biological and clinical situation allowing evaluation of intrinsic chemosensitivity. We assess the fotemustine (F) (100 mg/m^2 day 1)/ cisplatin (CDDP) (33 mg/m^2 days 1–3)/etoposide (VP16) (75 mg/m^2 days 1–3) monthly regimen for efficacy in non-removable glioblastomas at presentation. Between 1995 and 1998, 33 consecutive patients with symptomatic non-removable histologically proven glioblastomas were treated; none of them had previously received chemotherapy, irradiation or surgical debulking. Objective response was evaluated by contrast enhancement with magnetic resonance imaging (MRI) scan after each treatment. Toxicity was moderate and mainly haematological (grade III–IV thrombopenia = 20/171 cycles; leucopenia = 25/171). Neutropenic fever was rare and no intracranial haemorrhages or treatment-related deaths were noted. Nausea and vomiting (grade I), and asymptomatic hearing loss were common. Peripheral neuropathy occurred in 3 patients. Objective response rates were 9/33 (27%) (stabilisation = 17/33). Mean survival time was 14.4 (11.2 months in the 26 deceased patients) with a median survival of 10 months. Median survival rates at 6 and 12 months were 88% and 42%, respectively. 7/33 patients are still alive with median survival of 34.6 months. 7/33 (4/7 alive) were long-term survivors (range: 19–67 months). Neoadjuvant chemotherapy in non-resectable patients is safe allowing delayed RT. Phase II chemotherapy trials should include studies with a subgroup of non-resectable tumours.

Keywords: Chemotherapy; Glioblastomas

1. Introduction

The prognosis for patients with malignant gliomas has not significantly changed in recent years. Despite debulking surgery, radiation and cytotoxic chemotherapy, median survival duration is 4–12 months and virtually no patients are cured of their illness [1]. Recent studies suggest that the incidence of high-grade gliomas is rising, particularly in the elderly and the majority of these are glioblastomas. In the literature, chemotherapy has a limited impact on the survival of these patients [2–5]. Most chemotherapy trials using different routes and agents in this disease have relied on lipid-soluble agents that pass through the blood–brain barrier that is routinely exploited by neuroimaging studies [6]. Nevertheless, neuro-oncologists know that some gliomas respond to chemotherapy, but they cannot predict which ones. Some evidence has been put forward for oligodendrogliomas and mixed gliomas [7] but nobody knows which astrocytic gliomas and glioblastomas respond to chemotherapy and why [8].

Fotemustine (diethyl 1-(3-(2 chloroethyl) 3 nitrosoureido) ethyl phosphonate) is an alkylating agent characterised by the grafting of a phosphonoalanine group

* Corresponding author. Tel.: +33-4-92-03-77-44; fax: +33-4-92-03-79-07.

0959-8049/00/$ - see front matter
PII: S0959-8049(00)00048-4

onto the nitrosourea radical with consequent high lipophilia and improved diffusion through the cell membrane and the blood–brain barrier [9]. Fotemustine, cisplatin (CDDP) and etoposide (VP16) are all efficacious in astrocytoma [10] and their toxicity profiles suggest that it should be possible to administer them together in full doses. A preliminary large phase II study was conducted at the Antoine Lacassagne centre in Nice on 73 adult patients treated with fotemustine, 100 mg/m^2 once weekly for 3 weeks and maintenance with 100 mg/m^2 every 3 weeks, on responding or stabilised patients after a 5-week rest period. A 22.2% response rate was obtained in 63 evaluable patients, with a median duration response of 28 weeks [11]. An objective response and stabilisation were reported for 74% of patients with a median overall survival duration of 40 weeks. The association of fotemustine and radiotherapy was also tested. Radiotherapy of 60 Gy was delivered to the whole brain during the 5-week rest interval after induction with fotemustine 100 mg/m^2 for 3 weeks. The response rate obtained was 27.1% with a median survival of 39 weeks for responders and stabilised patients [12]. This treatment was associated with thrombocytopenia (27.1%), leucopenia (25.4%) and nausea and vomiting (24.7%). Peripheral neuropathy and hearing loss were dose-limiting. A high-dose of intravenous CDDP demonstrated substantial activity against malignant gliomas recurrent after nitrosourea failure [13].

In this study, we aim to assess the efficacy of polychemotherapy and radiotherapy in a neoadjuvant setting.

2. Patients and methods

Adults with newly diagnosed glioblastomas were given two to six 1 monthly cycles of the same chemotherapy regimen followed by radiation therapy. To estimate the response rate to chemotherapy, survival at 6, 9 and 12 months, and toxicity of this combined modality approach in glioblastomas was measured.

2.1. Patient population

Patients were eligible for treatment with this regimen if they met the following criteria: (1) were >18 years of age with histologically confirmed glioblastomas; (2) had normal haematological white blood cell (WBC count $>4000/\mu l$ and platelet count $>100\,000/\mu l$), renal and hepatic functions; (3) had received no prior antineoplastic therapy (i.e. debulking surgery, radiotherapy or chemotherapy). World Health Organisation (WHO) Performance Status was not a determinant criterion. The pathology and grade of the tumour were determined at the Department of Anatomopathology of the Pasteur Hospital in Nice and were reviewed independently by two pathologists. Anaplastic astrocytoma, mixed glioma and anaplastic oligodendroglioma were excluded. No time-frame between biopsy and the start of chemotherapy was specified.

2.2. Chemotherapy

All patients were hospitalised at the Antoine Lacassagne centre for chemotherapy administration after surgery. Hydratation, which consisted of 2.5 l of 5% glucose, was given each day of chemotherapy. A total of two to six 1 monthly cycles of fotemustine (100 mg/m^2.day 1)/CDDP (33 mg/m^2.days 1–3)/VP16 (75 mg/m^2.days 1–3) was planned. All patients had single-lumen central catheters. Delays for administration of chemotherapy were allowed and treatment was postponed for 1 week if the total WBC count was less than 3000/μl or platelet count was less than 100 000/μl. Chemotherapy treatments were discontinued and radiation therapy was initiated if a patient had progressive disease on clinical or radiological evaluation [14] according to MacDonald criteria.

Antiemetic treatment (intravenous ondansetron 8 mg) was systematically administered. Dexamethasone or methylprednisolone were not used as anti-emetics because of their effects on the blood–brain barrier. The doses of methylprednisolone used to control brain oedema were kept as constant as possible to ensure that changes or magnetic resonance imaging (MRI) scans used to determine tumour response or progression were not related to changes in glucocorticoid doses.

2.3. Radiation therapy

Radiation therapy was administered at the Antoine Lacassagne centre using a dose and schedule that were routine for patients with glioblastomas. The initial target volume included the preoperative volume of enhancement on computed tomography (CT) and the surrounding area of brain oedema with a 2 cm margin. This region received 60 Gy administered on consecutive weekdays for 6 weeks. The final fractions were administered to a smaller volume that included the contrast-enhancing tumour. The total radiation dose to this region was 60 Gy in 2 Gy/fraction over 6 weeks.

2.4. General medical measures

All patients had weekly monitoring of haematology profiles. Platelet transfusions were administered to maintain a platelet count greater than 20 000/μl. Oral methylprednisolone was prescribed to maintain peritumoral brain oedema as stable as possible. Anticonvulsant levels (phenytoin, valproic acid or carbamazepine) were monitored bimonthly.

2.5. Measurement of responses and survival

Responses to chemotherapy and radiotherapy portions were determined by comparing the contrast-enhanced MRI scans and neurological examinations performed before the initiation of chemotherapy with those performed after every two cycles of chemotherapy. The following response criteria were used to evaluate the efficacy of treatments [14]. Tumour size was defined as the product of the two largest perpendicular tumour diameters. CT scan was performed before biopsy; MRI scans were performed after biopsy, every two cycles of chemotherapy, radiotherapy or when a neurological event occurred. A complete response (CR) was defined as the complete disappearance of all contrast-enhancing tumours in a patient with a stable dose of glucocorticoid, and with a stable or improving neurological examination. A partial response (PR) required a $>50\%$ reduction in the contrast-enhancing tumour size with a stable dose of glucocorticoid, and a stable or improving neurological examination. Progressive disease (PD) was defined as a greater than 25% increase in the size of the contrast-enhancing tumour or progressive neurological abnormalities on stable or increasing glucocorticoids. Stable disease (SD) consisted of those patients whose clinical status and CT or MRI sizes did not meet the criteria for CR, PR or PD.

2.6. Measurement of toxicities

History, physical examination, haematology and chemistry profiles were obtained before each cycle of chemotherapy. Toxicities from the chemotherapy portion of the study were quantified using the National Cancer Institute common toxicity criteria.

2.7. Statistical analysis

The primary statistical endpoint was the determination of the response rate to polychemotherapy regimen. Survival was measured from the date of diagnosis.

3. Results

3.1. Patient characteristics

33 patients with newly diagnosed glioblastomas were operated upon in the Pasteur Hospital and treated at the Antoine Lacassagne centre in Nice from 1995 to 1998. All patients received chemotherapy, radiation therapy and follow-up evaluation at the Antoine Lacassagne centre and Neurological Department (Pasteur Hospital).

Patients ranged in age from 20 to 73 years (median: 57.7 years). 28 (85%) were over 45 years. 20 patients were male (61%) and 31 (94%) were caucasian. All had non-resectable glioblastoma multiforme diagnosed by needle biopsy. Most patients began chemotherapy within 4 weeks following biopsy (Table 1). WHO Performance Status was $\geqslant 2$ for 17 patients (52%) and <2 for the other 16 patients (49%).

3.2. Treatment delivered

All patients had two cycles of polychemotherapy after biopsy, 8 (24%) completed 4 cycles, and 10 (30%) had 5–6. 26 patients (79%) completed radiotherapy; 4 patients (12%) died during radiotherapy; 3 are still in the first line of polychemotherapy. 12 patients (60%) stopped polychemotherapy on account of haematological toxicity after two cycles. All had concomitant treatment with valproic acid (1000–1500 mg/day) and antiepileptic treatment was changed for phenytoin, carbamazepine or vigabatrin. No haematological problem resulted from further cytotoxic treatments.

3.3. Response

Tumour sizes before and after chemotherapy were calculated on the two greater axis products for all patients. All patients had measurable disease on MRI scans.

The objective response rate was 9/33 (27%) with 1 CR and 8 PR. Stabilisation was obtained for 17/33 patients (52%). Median time to progression after radiotherapy was 6.8 months for stable and responding patients.

7 patients (21%) had evidence of PD during chemotherapy (mean age: 57 years). Median survival of this subgroup was 4.8 months. None of them were stabilised with radiotherapy.

Table 1
Clinical characteristics of patients with non-removable glioblastomas

Patient characteristics	
Age (years)	
Median (range)	57.7 (20–73)
	n (%)
Male	20 (61)
Location	
Frontal	5 (15)
Temporal	11 (33)
Parietal	10 (30)
Other	7 (21)
WHO performance status	
$\geqslant 2$	17 (52)
<2	16 (49)
Survival (months)	
Median	10
Mean	14.4
Range	4–67

3.4. Survival

Mean survival duration was 14.4 months for the whole group (11.2 months in the 26 deceased patients), with median survival 10 months (Fig. 1). Mean and median survival rates were different because of long-term survivors. Median survival rates at 6 and 12 months were 88% and 42%, respectively.

7/33 (4/7 alive) were considered as long-term survivors (>18 months; range: 19–67 months). The mean age of long-term survivors was 57.9 years. Age was not a determinant of survival but 5/7 glioblastomas in long-term survivors were located in frontal or temporal lobes. Another hypothesis is that all patients had primary glioblastoma. 5 patients lived more than 2 years (range: 2.5–5.7 years). On average follow-up of 3 years, 7/33 patients are still alive with median survival 34.6 months. 9 patients had second-line chemotherapy.

3.5. Toxicities

Toxicity was moderate and mainly haematological. Neutropenic fever was rare and no intracranial haemorrhages or treatment-related deaths were noted. Nausea, vomiting and peripheral neuropathy were rare. No patient had deep venous thrombosis or pulmonary emboli requiring anticoagulation.

Myelosuppression was particularly common with the nadir of WBC and platelets occurring 16 days after initiation of chemotherapy. Haematological grade III–IV toxicity was observed for 12/33 patients (36%). All of them had anti-epileptic treatment with valproic acid. Grade III–IV leucopenia appeared in 25/171 cycles without neutropenic fever. Grade III–IV thrombopenia was observed in 20/171 cycles but no patient required platelet transfusion. Nausea and vomiting (grade 1) occurred in 85% of patients despite treatment with intravenous ondansetron. Seventy per cent of patients complained of asthenia and anorexia for 1 week following the course and these symptoms increased with the number of courses. A cisplatin-induced peripheral neuropathy occurred in 3 patients. This condition was generally mild and did not require discontinuation of chemotherapy. An audiogram was systematically performed before and after chemotherapy. The majority of patients had asymptomatic high-frequency hearing loss; only 1 became symptomatic.

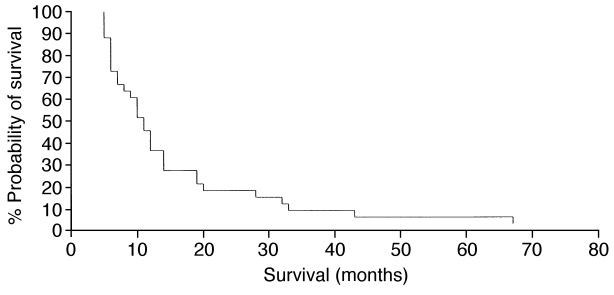

Fig. 1. Kaplan–Meier curve: survival of glioblastomas in neoadjuvant setting.

4. Discussion

Chemotherapy is often the only therapeutic opportunity for recurrent gliomas [4]. Nitrosoureas are the standard treatment for these tumours. The response rates published in phase II studies with different nitrosoureas (carmustine, lomustine, fotemustine) are difficult to compare and to interpret because the evaluation criteria in previous reports did not always include CT scans in which different types of high-grade gliomas were mixed. The concentration of intravenously administered water-soluble contrast agents within brain tumours, as imaged and measured by computerised or magnetic resonance studies, increases as these compounds pass from the systemic circulation through the disrupted blood–brain barrier into the brain tumour [15]. Neoangiogenesis (contrast enhancement) is the main criterion used to quantify response to treatments. Benefits from the use of chemotherapy were suggested by the BTSG phase III randomised trial results in an adjuvant setting after surgical procedure, in combination with radiotherapy [3]. In this trial the proportion of survivors at 18 months was 19% for patients treated with carmustine and radiotherapy versus 4% for patients treated with radiotherapy alone. Hildebrand and the EORTC brain tumour study group, in a phase III study, proved that nitrosourea, associated with surgery and radiotherapy, prolonged survival [16]. The majority of studies have included a number of different histological types, each one with biologically distinct behaviour as has been demonstrated by the different natural histories and responses to therapy [7].

This study suggests that the combination of fotemustine, CDDP and VP16 produces a significant response rate in non-removable glioblastomas. These results agree with previous work [5,17,18], using approximately the same treatment. The lack of clinical or radiological progression in non-resectable glioblastomas during chemotherapy suggests that this regimen is active. These findings contrast sharply with those from recent monotherapy studies with paclitaxel [19] or temozolomide [20] given to a virtually identical patient population. Forty per cent of these patients developed clinical or radiological progression after the first month of paclitaxel therapy. Fifty per cent of non-resectable patients had only one cycle of temozolomide. Comparison with other studies reveals that the populations cannot be compared on account of different surgical resection procedures, and mixed histologies. If we analyse different results on a subpopulation of non-removable, non pretreated

glioblastomas, polychemotherapy seems to have an impact on survival. For Pouillart and colleagues [21], introduction of chemotherapy at the early stage of disease in non-removable glioblastomas can be relevant. It was confirmed by Gruber and associates [22] and Lassen and coworkers [17] with other chemotherapy regimens. In the series of Grossman and colleagues [5], 71% of patients had formal debulking surgery procedure but 83% of all patients had assessable residual tumour. This work led to the setting-up of an Eastern Cooperation Oncology Group and Southwest Oncology Group, to a phase III study that compares carmustine (BCNU) and CDDP with standard radiation and adjuvant BCNU in newly diagnosed glioblastomas. In our data, changes in tumour volume and enhancement are used to determine the response status of non-resectable glioblastomas (overall response rate — ORR: 27%). Grossman and colleagues found 19% of patients were long-term survivors in their population [5] compared with 4 (12%) in our series. The ages of the patients were not significantly different. The overall survival rate was 45% at 1 year, 19% at 2 years and 10% at 3 years compared with 42, 15 and 9% in Grossman's study.

In most other studies, histologies involved mixed high-grade gliomas (glioblastomas and AA) and initial surgical procedures are pooled (gross total, partial resections and biopsy only). Curran and associates used a recursive partitioning technique to analyse survival in 1578 patients entered in three Radiation Therapy Oncology Group malignant glioma trials from 1974 to 1989 that administered several radiation therapy regimens with and without chemotherapy [1]. The most significant split occurred by age ($\geqslant 50$ versus < 50 years). Eight variables were significantly predictive of survival: histology, age, neurological function, prior surgery, mental status, time from first symptom, motor deficit and memory lag. For patients aged 50 years and older, performance status was the most important variable. Median survival times were 4.3–58.6 months for the six subgroups. Patients with non-resectable glioblastomas over the age of 50 years as for the majority of our patients should correspond to the subgroup with a median survival time of 4.3 months.

In the recurrent setting, after surgery (gross or partial resection) and radiotherapy, if we look for results of first-line chemotherapy, the literature is very difficult to analyse because of the mixture of type of surgery, histology and chemotherapy regimen (Table 2). Despite the difficulties, it can be concluded that only a subpopulation of glioblastomas is able to receive maximum combination (surgery, chemotherapy and radiotherapy) and, where possible, chemotherapy before radiation. It is very difficult to identify which chemotherapy will be effective on patients who have already progressed after radiation therapy. At recurrence after initial surgery and radiation, patients with malignant gliomas are often offered a second surgical resection as part of the treatment plan for their tumour recurrence. Survival after a second resection remains poor despite advances in imaging, operative technique and adjuvant therapies [27]. Younger age and more extensive initial resection, but not Karnofsky Performance Scale score at the time of diagnosis or recurrence, predicted a higher chance of selection for re-operation. The median survival period after first tumour progression is 29 weeks for re-operated patients versus 23 weeks otherwise. For high-grade gliomas, the percentage of long-term survivors is low and fewer than 3% live more than 5 years [28].

This polychemotherapy regimen appears to have significant activity and may prolong survival in adults with non-removable newly diagnosed glioblastomas. Cytostatic agents could be associated with standard treatments. The study demonstrates that it is possible to administer chemotherapy before radiation therapy without an adverse impact on survival in adults with non-operable glioblastomas. Whilst this type of chemotherapy

Table 2
Data in recurrent setting for glioblastomas after surgery and radiotherapy[a]

Authors [Ref.]	No.	Histology	Surgery	Results	Cytotoxic
Levin [23]	88	37 GB 38 AA 13 others	ND	PR + SD 61%	Thioguanine PCZ, DBD BCNU, 5-FU, HU
Trandafir [24]	25	10 GB 3 AA 12 others	ND	PR 36% SD 20%	Fotemustine + PCZ
Pierga [25]	29	24 GB 5 AA	33% GTR	PR 27% SD 17.2%	PCZ, VCR, MT F/CDDP/VCR 5-FU, TP, LO
Van Den Bent [26]	13	7 GB 4 AA	ND	SD 7.6%	CDDP, VP16
Frenay (this study)	17	All GB	64.7% GTR	SD 41.2%	F, CDDP, VP16

[a] AA, anaplastic astrocytoma; GB, glioblastoma; GTR, gross total resection; PR, partial response; BO, biopsy only; BCNU, carmustine; VP16, etoposide; CDDP, cisplatin; RXT, radiotherapy; HGG, high-grade glioma; F, fotemustine; DBD, dibromodulcitol; 5-FU, 5 fluorouracil; LO, lomustine; MT, mechlorethamine; TP, teniposide; HU, hydroxyurea; PCZ, procarbazine; VCR, vincristine; ND, not done.

apparently produces some responses when used as first-line treatment, no conclusion can be made regarding survival without a randomised prospective study. Combination regimens, whereby biological agents synergise with either radiation or chemotherapy to achieve maximal efficacy, may translate into improved results in the clinical population. This procedure can facilitate the recognition of inactive agents or regimens. Survival benefit and tumour response are probably related. Optimal timing, doses, schedules and methods of chemotherapy delivery must be determined for patients who will benefit from treatment, whereas those with resistant tumours should receive novel therapies early on.

Acknowledgements

We want to thank Dr B. Giroux (Servier) and Professor Brucher, Professor Chatel and Professor Michiels for their analysis in neuropathology.

References

1. Curran WJ, Scott CB, Horton J, *et al*. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* 1993, **85**, 704–710.
2. Walker MD, Alexander E Jr, Hunt WE, *et al*. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. *J Neurosurg* 1978, **49**, 333–343.
3. Walker MD, Green SB, Byar DP, *et al*. Randomized comparison of radiotherapy and nitrosoureas for the treatment of malignant gliomas after surgery. *N Engl J Med* 1980, **303**, 1323–1329.
4. Fine HA, Dear BG, Loeffler JS, Black P, Carnellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993, **71**, 2285–2297.
5. Grossman SA, Wharam M, Sheidler V, *et al*. Phase II study of continuous infusion carmustine and cisplatin followed by cranial irradiation in adults with newly diagnosed high-grade astrocytoma. *J Clin Oncol* 1997, **15**, 2596–2603.
6. Lesser GJ, Grossman S. The chemotherapy of high-grade astrocytomas. *Semin Oncol* 1994, **21**, 220–235.
7. Cairncross JG, Macdonald DR. Successful chemotherapy for recurrent malignant oligodendroglioma. *Ann Neurol* 1988, **23**, 360–364.
8. De Angelis LM, Burger PC, Green SB, *et al*. Adjuvant chemotherapy for malignant glioma: who benefits? *Ann Neurol* 1996, **40**, 491–492.
9. Raymond E, Haon C, Boaziz C, Coste M. Logistic regression model of fotemustine toxicity combining independent phase II studies. *Cancer* 1996, **78**, 1980–1987.
10. Tirelli U, D'incalci M, Canetta R, *et al*. Etoposide (VP-16-213) in malignant brain tumors: a phase II study. *J Clin Oncol* 1994, **2**, 432–437.
11. Frenay M, Giroux B, Khoury S, *et al*. Phase II study of fotemustine in recurrent supratentorial malignant gliomas. *Eur J Cancer* 1991, **27A**, 852–856.
12. Biron P, Roux N, Chauvin N, *et al*. Phase I–II trial of high dose fotemustine followed by autologous bone marrow transfusion in high grade gliomas. *Eur J Cancer* 1991, **27A**, S191.
13. Spence AM, Berger MS, Livinston RB, Ali-Osman F, Griffin B. Phase II evaluation of high-dose intravenous cisplatin for treatment of adult malignant gliomas recurrent after chloroethylnitrosourea failure. *J Neuro Oncol* 1992, **12**, 187–191.
14. MacDonald DR, Cascino TL, Schold SC, *et al*. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990, **8**, 1277–1290.
15. Norman D, Stevens EA, Wings SD, *et al*. Quantitative aspects of contrast enhancement in cranial computed tomography. *Radiology* 1978, **129**, 683–688.
16. Hildebrand J, Sahmoud T, Mignolet F, Brucher JM, Afra D, and the EORTC brain tumor group. Adjuvant therapy with dibromodulcitol and BCNU increases survival of adults with malignant gliomas. *Neurology* 1996, **85**, 602–607.
17. Lassen U, Kristjansen PEG, Wagner A, Kosteljanetz M, Poulsen HS. Treatment of newly diagnosed glioblastoma multiforme with carmustine, cisplatin and etoposide followed by radiotherapy. A phase II study. *J Neuro Oncol* 1999, **43**, 161–166.
18. Yung WKA, Janus TJ, Maor M, Feun LG. Adjuvant chemotherapy with carmustine and cisplatin for patients with malignant gliomas. *J Neuro Oncol* 1992, **12**, 131–135.
19. Fetell MR, Grossman SA, Fisher JD, *et al*. Pre-irradiation paclitaxel glioblastoma multiforme: efficacy, pharmacology and drug interactions. *J Clin Oncol* 1997, **15**, 3121–3128.
20. Friedman HS, McLendon RE, Kerby T, *et al*. DNA mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to temodal in newly diagnised malignant glioma. *J Clin Oncol* 1998, **16**, 3851–3857.
21. Pouillard P, Mathe G, Huguenin P, *et al*. Treatment of inoperable glioblastomas using a combination of adriamycin, VM 26 and CCNU. *Bull Cancer* 1977, **64**, 125–136.
22. Gruber ML, Glass J, Choudhri H, Nirenberg A. Carboplatin chemotherapy before irradiation in newly diagnosed glioblastoma multiforme. *Am J Clin Oncol* 1998, **21**, 338–340.
23. Levin VA, Prados M. Treatment of recurrent gliomas and metastatic brain tumors with polydrug protocol designed to combat nitrosourea resistance. *J Clin Oncol* 1992, **10**, 766–771.
24. Trandafir L, Da Costa L, Borel C, *et al*. Fotemustine and oral procarbazine combination regimen in the treatment of recurrent gliomas. *Proc Am Soc Clin Oncol* 1995, **14**, 149.
25. Pierga JY, Jouve M, Laurence V, *et al*. Sequential polychemotherapy in recurrent malignant gliomas: a phase II study. *J Neuro Oncol* 1998, **39**, 183.
26. Van Den Bent MJ, Pronk L, Sillevis Smith PAE, *et al*. Cisplatin etoposide chemotherapy in recurrent gliomas. *J Neuro Oncol* 1998, **39**, 184.
27. Barker FG, Chang SM, Gutin PH, *et al*. Survival and functional status after resection of recurrent glioblastoma multiform. *Neurosurgery* 1998, **42**, 709–721.
28. Salvati M, Cervoni L, Artico M, Caruso R, Gagliari FM. Long-term survival in patients with supratentorial glioblastoma. *J Neuro Oncol* 1998, **36**, 61–64.