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Original Paper

A Retrospective Study of the Value of Chemotherapy as Adjuvant Therapy to Surgery and Radiotherapy in Grade 3 and 4 Gliomas

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The aim of this retrospective study was to evaluate the effect of adjuvant chemotherapy among patients < 55 years of age with anaplastic gliomas (histological grade 3, $n = 85$) with four cycles 4 weeks apart of 160 mg carmustine (BCNU) infused into the internal carotid artery, combined with vincristine 2 mg and procarbazine 50 mg×3 for 1 week (i.a.BCNU–PV) versus no adjuvant chemotherapy. In glioblastomas (histological grade 4, $n = 257$) the same chemotherapy was evaluated versus two cycles 4 weeks apart of 160 mg lomustine (CCNU) orally instead of BCNU, combined with vincristine and procarbazine (PCV) versus no chemotherapy. All patients in both groups received radiotherapy. Among glioblastoma patients < 55 years of age there was a significant ($P = 0.03$), but moderately increased survival in the i.a.BCNU–PV group versus the two other arms that did not differ from each other. This difference could be explained by an uneven distribution of prognostic factors, especially age group (< 50 years versus 50–54 years) in favour of the i.a.BCNU–PV group. In anaplastic gliomas, the median survival in the i.a.BCNU–PV group was 80 months versus 25 months for the no chemotherapy arm ($P = 0.004$). No significant differences in the distribution of prognostic factors were found between the two therapy arms. We suggest that the role of adjuvant chemotherapy in glioblastomas is unclear, while i.a.BCNU–PV as adjuvant chemotherapy among patients < 55 years of age and with anaplastic gliomas increased survival markedly. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

AT PRESENT there are three main modalities available for the treatment of malignant brain tumours. The best available non-experimental strategy consists of neurosurgical intervention with total or subtotal resection of tumour tissue. Because of the infiltrative nature of these tumours, surgery is followed by local radiotherapy with a total tumour dose of approximately 50 Gy [1, 2]. Several studies [3–5] have demonstrated a significant survival advantage for patients receiving postoperative radiation. Despite numerous randomised trials [6–12], some with a substantial number of patients, for more than 20 years follow-up, it has been difficult to prove the value of adjuvant chemotherapy. In a meta-analysis [13], using results from 16 randomised trials involving more than 3000 patients, the authors concluded that chemotherapy is advantageous for malignant gliomas and should be considered part of the standard therapeutic regimens. This was a compilation of patients treated in many different ways; intra-arterial, intravenous and oral chemotherapy with different drugs, schedules and doses.

In most studies, tumours are a mixture of histological grade 3 (anaplastic gliomas) and grade 4 (glioblastomas). These tumours have different prognoses; in anaplastic brain tumours, median survival is approximately 2 years or more, with a third or more of the patients alive after 5 years [14–16], while patients with glioblastomas have a median survival of approximately 1 year and patients only exceptionally live for 5 years [17]. Many of the studies were small. Regardless of these considerations, adjuvant chemotherapy, usually with a

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nitrosourea, is frequently employed [4] for both grade 3 and 4 gliomas.

Few centres, or even co-operative study groups, have enough patients to do randomised studies. To some extent, we are, therefore, forced to consider retrospective studies, incorporating prognostic factors to make groups comparable, in order to make decisions with regard to future adjuvant chemotherapy. We, therefore, conducted a retrospective study of survival in comparable groups with regard to prognostic factors, treated with or without adjuvant chemotherapy, at The Norwegian Radium Hospital, since the introduction of modern diagnostic methods such as computed tomography (CT) scans or magnetic resonance imaging (MRI). Some of the data, comprising 79 patients with grade 3 (19 patients) and grade 4 (60 patients) tumours have been published previously [18].

PATIENTS AND METHODS

Between 1980–1995 we treated 137 patients with anaplastic, histological grade 3 tumours and 512 patients with glioblastoma multiforme (histological grade 4 tumours). Tumours were macroscopically resected when possible, or only a biopsy taken. More than 90% had tumour resection. Most patients were operated upon at neurosurgical departments at the National Hospital or Oslo City hospital. The time of diagnosis was defined as the radiological (CT or/and MRI) date of diagnosis, and survival was measured from that date until death. Histopathology was evaluated according to WHO criteria [19].

Radiotherapy

All patients included in the analysis received radiotherapy. In the glioblastoma group, 20 chemotherapy (PCV) patients, and 1 patient in the no chemotherapy group, received brachytherapy to 60 Gy over 5 days. The accumulated dose of radiotherapy in the groups are given in Table 1.

Chemotherapy

During the time span of 15 years, treatment policy has changed. Patients received lomustine (CCNU) 160 mg orally, or 160 mg of carmustine (BCNU) intra-arterially (i.a.) in the internal carotid artery on the ipsilateral side of the tumour, in both cases combined with vincristine 2 mg intravenously (i.v.) on day 1 and procarbazine 50 mg×3 days 2–8. When CCNU was given (orally) the chemotherapy was named PCV, when BCNU was given it was named i.a.BCNU–PV. When PCV was given, patients received two cycles 4 weeks apart and then irradiation. Patients usually received PCV at the local hospital and were admitted to our hospital approximately 12 weeks after the first course. Patients that had disease progression during this time were normally not admitted into our institution for radiotherapy.

Table 1. *Accumulated radiation doses in Gy in anaplastic gliomas according to chemotherapy*

Chemotherapy	Anaplastic gliomas	Glioblastoma
i.a.BCNU–PV	52.3 ± 4.7	50.6 ± 8.4
PCV	56.3 ± 10.3	51.4 ± 6.4
No chemotherapy	52.7 ± 4.2	48.6 ± 8.1

i.a.BCNU–PV, intra-arterial carmustine, with vincristine and procarbazine; PCV, oral lomustine, with vincristine and procarbazine.

Among brachytherapy patients, PCV was given after irradiation. When patients received i.a.BCNU–PV, a total of four cycles were given every fourth week and radiation initiated 4 weeks after the last cycle—i.a.BCNU–PV was administered through a catheter introduced through the femoral artery and placed in the internal carotid artery at the level of the first cervical vertebra. Premedication consisted of 0.5 ml Leptanal (fentanyl 0.1 mg/ml). From day 1, patients received dexamethasone 4 mg×4 which was descalated over 10 days. Two hundred milligrams of BCNU powder was dissolved in 1 ml 96% ethanol and then added to 49 ml normal saline solution immediately prior to infusion. The solution was then infused automatically with a pressurised injector type. Of the total 50 ml volume, 40 ml was administered over 20 min. If the patient experienced eye pain during the infusion, a cold, wet cloth was applied over the eye and, if necessary, 0.5–1 ml of Leptanal (i.v.) was given.

All chemotherapy doses were expressed in total dose, not per m^2.

i.a.BCNU–PV was only given to patients < 55 years of age. For comparison, all survival curves are, therefore, only calculated for patients < 55 years of age. Some patients did not receive chemotherapy.

As a rule patients were evaluated with CT scans and neurological examination before radiation and 3 months after radiation at our hospital, but more often at the local hospital or other centres of oncology.

This was not a randomised study. Prognostic factors in the total group of anaplastic gliomas ($n = 137$) and glioblastomas ($n = 512$) were, therefore, identified. Since for survival curves only patients < 55 years of age were considered, the values for age as a prognosticator have been calculated for patients < 50 years versus 50–54 years. To assess the importance of individual prognostic factors, survival was calculated by the Kaplan–Meier method and differences between survival curves tested with the Logrank test [20] (univariate analysis). The percentage of each prognostic factor among patients < 55 years of age was then calculated for the different groups representing the survival curves. Possible differences between the groups were tested by the chi-square test.

Also, we compared survival curves for both chemotherapy and no chemotherapy groups during the years 1980–1987 as compared with patients treated from 1998 to 1995. There were no differences between comparable groups treated at different time intervals ($P = 0.54$ for both comparisons).

RESULTS

The variables tested for prognostic value are listed in Table 2 with median survival value for each subset and the corresponding P value from the Logrank test, both for anaplastic gliomas and glioblastomas. Significant ($P < 0.05$) prognostic factors by univariate analysis were age group < 50 years versus 50–54 years among glioblastoma patients, but not for anaplastic gliomas. Other prognosticators were performance status (0–2 versus 3–4), dexamethasone dependency, defined as being on dexamethasone at admittance, focal signs, behavioural ('mental') changes and epilepsy as the first symptom. Nausea/vomiting (at admittance), sex, T-category, or visual disturbances were not significant prognostic factors.

Among glioblastoma patients, there was an inbalance in age group ($P < 0.0001$ versus PCV group, $P = 0.001$ versus no chemotherapy group), with a younger median age for the i.a.BCNU–PV group. In addition there was an inbalance

Table 2. Univariate survival analysis in anaplastic gliomas (n = 137) *and glioblastomas* (n = 512)

Variables	Anaplastic gliomas		Glioblastomas	
	Median survival (months)	Log-rank test (*P* value)	Median survival (months)	Log-rank test (*P* value)
Age (years)				
< 50	42	0.8	15	0.006
50–54	42		11	
Performance status				
0–2	45	< 0.0001	14	< 0.0001
3–4	12		8	
Dexamethasone dependency				
No	46	< 0.0001	14	< 0.0001
Yes	12		9	
Focal signs				
No	45	0.0002	13	0.0002
Yes	20		11	
Behavioural ('mental') changes				
No	46	0.002	14	0.005
Yes	23		11	
First symptom epilepsy				
No	23	0.04	12	0.002
Yes	42		13	

Table 3. Some characteristics of patients with glioblastomas (histological grade 4)

Variable	i.a.BCNU–PV (*n* = 100) (%)	PCV (*n* = 65) (%)	No chemotherapy (*n* = 92) (%)
Age (years) (median, range)	43 (21–54)	47 (21–54)	44 (20–54)
Age group (years)			
< 50	90	63★	70†
50–54	10	37	30
Performance status (ECOG)			
0–2	86	78	80
2–4	14	22	20
Dexamethasone dependency			
No	62	41‡	57
Yes	38	59	43
Focal signs			
No	63	69	61
Yes	37	31	39
First symptom epilepsy			
No	38	48	45
Yes	62	52	55
Behavioural ('mental') changes			
No	56	49	46
Yes	44	51	54

i.a.BCNU–PV, intra-arterial carmustine, with vincristine and procarbazine; PCV, oral lomustine, with vincristine and procarbazine. ★*P* < 0.0001 (versus i.a.BCNU–PV). †*P* = 0.001 (versus i.a.BCNU–PV). ‡*P* = 0.02 (versus i.a.BCNU–PV).

(*P* = 0.02), with regard to dexamethasone dependency, with fewer patients dependent in the i.a.BCNU–PV group compared with the PCV group (Table 3). The i.a.BCNU–PV group was, therefore, expected to have a better survival as compared with the other two groups. We found a moderate, but significant difference in survival between the i.a.BCNU–PV, and both the PCV and no chemotherapy groups, which did not differ from each other (Figure 1). The median survival in months was 16 (95% confidence interval (CI) = 14–20), 12 (CI = 12–18) and 12 (CI = 11–15), respectively.

In the anaplastic glioma group, there were only 12 PCV patients. Since no meaningful analysis of prognostic factors could be made for this group they were omitted. The distribution of significant prognostic factors in the other two therapy arms is shown in Table 4. No statistical differences in distribution of variables between groups were identified. In the i.a.BCNU–PV group of anaplastic gliomas, there were 45 anaplastic astrocytomas, two anaplastic oligodendrogliomas and five anaplastic mixed gliomas. In the no chemotherapy group, the corresponding subgroups were 10 anaplastic astrocytomas, 12 anaplastic oligodendrogliomas and 11 anaplastic mixed gliomas. The median survival within subgroups was 33 months for anaplastic oligodendrogliomas versus 26 months for the two other subgroups. This was not statistically significant (*P* = 0.23). In the i.a.BCNU–PV group, 40 (77%) underwent resection of the tumour, while 12 (23%) had a biopsy only. The corresponding figures in the no chemotherapy arm were 31 (94%) and 2 (6%).

There was a significant difference in survival for the i.a.BCNU–PV group (median survival 80 months, 95% CI 48–112) versus the no chemotherapy group (median survival 25 months, 95% CI 18–32), a difference of 55 months (Figure 2). The median survival for the 12 PCV patients was 36 months.

Toxicity

There was one serious complication (probably) due to i.a.BCNU–PV, with serious loss of vision of the ipsilateral eye. In a study by Shapiro and colleagues [21] a much higher incidence of serious complications, such as irreversible encephalopathy and visual loss, were observed. This could have been caused by the much higher dose of BCNU (200 mg/m^2) as opposed to our fixed dose of 160 mg.

Most patients had periorbital pain during the infusion, usually within the last 10 min of infusion. In no case was it

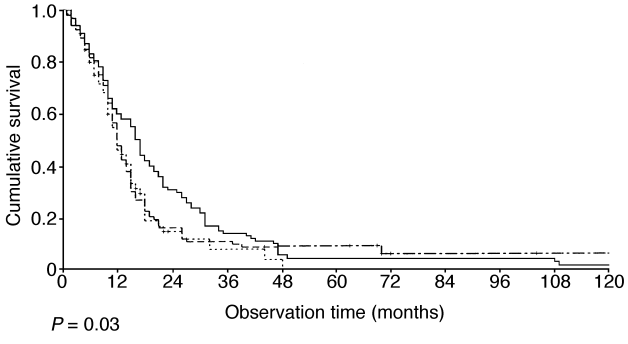

Figure 1. Survival in patients < 55 years of age with glioblastomas (histological grade 4 brain tumours) treated with intra-arterial carmustine, with vincristine and procarbazine (i.a.BCNU–PV) (*n* = 100), oral lomustine, with vincristine and procarbazine (PCV) (...*n* = 65) or no chemotherapy (- - - *n* = 92).

Table 4. Some characteristics of patients with anaplastic (histological grade 3) brain tumours

Variable	i.a.BCNU–PV ($n=52$) (%)	No chemotherapy ($n=33$) (%)
Age (years) (median, range)	39 (20–53)	39 (20–54)
Performance status (ECOG)		
0–2	96	85
2–4	4	15
Dexamethasone dependency		
No	79	69
Yes	21	31
First symptom epilepsy		
No	23	27
Yes	77	73
Behavioural ('mental') changes		
No	71	73
Yes	29	27
Focal signs		
No	71	64
Yes	29	36

i.a.BCNU–PV, intra-arterial carmustine, with vincristine and procarbazine.

necessary to stop the infusion, but in some cases the infusion was stopped for a short (1–2 min) time. Bone marrow depression causing serious infections, bleeding or postponement of a planned chemotherapy course did not occur either in the i.a.BCNU–PV group or the PCV group. Pulmonary fibrosis did not occur in our patients. There were no serious complications to the catheter procedure itself.

Serious brain damage, such as radionecrosis, occurred in 2 cases of the anaplastic glioma group and in 4 cases of the glioblastoma group. Otherwise, none had radiological signs of encephalopathy.

DISCUSSION

Most of the prognostic factors, such as age (< 50 years versus 50–54 years, see above), dexamethasone dependency, performance status, focal signs and epilepsy as first symptom, have been identified by others [22] for a mixture of grade III and IV astrocytomas. We also found behavioural changes to be a prognostic discriminator. This could reflect variations in survival depending on tumour location.

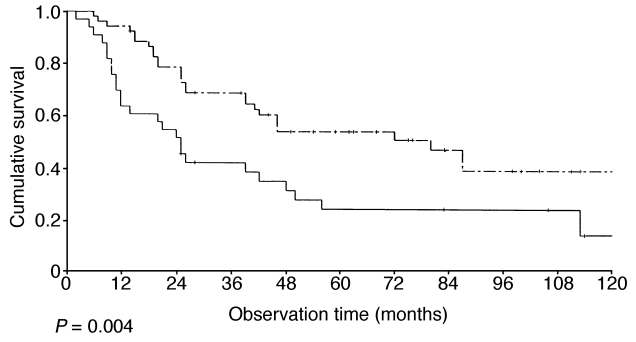

Figure 2. Survival in patients <55 years of age with anaplastic gliomas (histological grade 3 brain tumours) treated with intra-arterial carmustine, with vincristine and procarbazine (i.a.BCNU–PV) (- - - n=52) or no chemotherapy (—n=33).

In glioblastomas, the distribution of the prognostic factors were significantly different with regard to age group and dexamethasone dependency, in favour of the i.a.BCNU–PV group. The difference in age group probably reflects the clinicians attitude. A moderate difference in survival in favour of the i.a.BCNU–PV group versus PCV and the no chemotherapy groups, therefore, could be explained by selection bias, especially with regard to age group.

It is noteworthy that since patients that progressed on PCV normally were not admitted into our institution for radiotherapy there was a selection bias in favour of the PCV group in our series. It should also be noted that patients received only two courses of PCV versus four courses of i.a.BCNU-PV.

In anaplastic gliomas, among patients < 55 years of age, we found a significant and marked difference in survival in favour of patients treated with i.a.BCNU–PV before irradiation. There were only historical reasons for patient selection to i.a.BCNU–PV or to the no chemotherapy group. There was a fairly even distribution of prognostic factors between the two groups and no significant differences. It is to be noted that the distribution of histological subgroups clearly was not in favour of the i.a.BCNU–PV group. More patients in the no chemotherapy arm had tumour resection as compared with the i.a.BCNU–PV group. If anything, this should be unfavourable.

Although there are limitations for a non-randomised retrospective study, the data suggest that for adjuvant chemotherapy in patients with glioblastomas we have not been able to show any clear benefit, while in anaplastic gliomas i.a.BCNU combined with vincristine and procarbazine prior to irradiation in patients < 55 years of age, resulted in a significant and marked prolongation of median survival, in our study 55 months, with acceptable toxicity. The ability to extrapolate these data to older patients is limited, since prognosis in older patients is worse and more treatment-related complications could be expected. In order to confirm these, in our opinion, important data, we suggest a randomised study, for example, performed by the EORTC or cooperative groups in the U.S.A.

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