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Cisplatin Does Not Enhance the Effect of Radiation Therapy in Malignant Gliomas

EORTC Brain Tumor Group

The aim of this randomised trial was to test the effect of cisplatin given during radiation therapy in adults with supratentorial malignant gliomas. Of 285 patients included, 246 were evaluable. The main reasons for exclusion were: inadequate pathology or no pathology review (24 patients), exclusion of the institution (11 patients), and inadequate follow-up (4 patients). For 121 patients randomised to receive cisplatin 50 mg/m² on days 1, 8, 15 and 22 of radiation therapy, 81 were given the full dose. Radiation therapy alone was given to 125 control patients. All patients were followed until the recurrence of clinical signs (free interval) and until death (survival). Neither of these two parameters was modified by cisplatin. No signs of major toxicity were reported. It is concluded that at the doses used, cisplatin does not enhance the effects of radiation therapy in malignant gliomas.
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INTRODUCTION

RADIATION THERAPY has been repeatedly found to be an active adjuvant treatment in malignant brain gliomas prolonging the median survival by 30–100% [1]. In contrast, chemotherapy has increased the percentage of survivors at 18 and 24 months [2, 3] or the median survival [4] only in few studies; most of the trials have yielded negative results [1].

These observations provide a rationale for sparing the use of cytotoxic agents, such as nitrosoureas, for patients with signs of tumour recurrence, and for trying to enhance the efficacy of irradiation through the use of radiosensitisers.

A possible radiosensitisation effect of cisplatin has been shown *in vitro* in bacteria and in mammalian tumour cells, and *in vivo* in several animal models [5–7]. In addition, in human malignant gliomas, the drug has shown occasional antitumour activity when given intravenously, and an about 30% rate of partial remissions after intra-arterial administration [8].

The aim of the present trial was therefore to test the effects of cisplatin given as a radiosensitiser during radiation therapy of malignant gliomas.

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MATERIAL AND METHODS

The results reported in this trial are based on the analysis of 246 evaluable cases from a total of 285 patients included from September 1986 to October 1989.

39 patients were judged ineligible for the following reasons. In 24 the pathology was either inadequate (9 cases of which 7 patients proved to be low grade gliomas and 2 were considered non-glial tumours on pathology review), or no specimens were received for pathology review (15 cases). 11 patients belonged to 3 institutions which had to be excluded from the study for high number of inadequate follow-up. In 4 patients the follow-up was inadequate.

The criteria for patient selection were those used in our previous studies [9–11].

The diagnosis of malignant glioma (grade III or IV according to the WHO classification) based on histology, had to be confirmed by a central pathology reviewer (J.M. Brucher). Patients had to be aged over 15 years old. The neurological status after neurosurgery had to be equal or inferior to 3 on a functioning scale ranging from 1 to 4 (grade 4 patients being unable to perform even minimal normal activities, requiring hospitalisation and constant nursing care). The expected survival had to be superior to 8 weeks and patients had to show normal hematopoetic, renal, hepatic and cochlear functions, and no major medical illness.

Unlike in our prious trials intermittent administration of steriods during the free interval was tolerated.

All patients were irradiated within 7 weeks following neurosurgery, the mean delay being 24 days. A mean dose of 58 Gy were delivered to the tumour volume and an additional 2–3 cm margin, in 5 daily doses a week of 1.8 to 2 Gy per day, for

Table 1. Groups distribution of prognostic factors

Patients' characteristics	Group 1 (cisplatin plus radiotherapy)	Group 2 (radiotherapy alone)
No. included patients	142	143
No. evaluable patients	121	125
Age		
<45 yr	34 (28%)	37 (30%)
45–55 yr	34 (28%)	35 (28%)
>55 yr	53 (44%)	53 (42%)
Neurological score		
1	33 (27%)	32 (26%)
2	44 (36%)	62 (50%)
3	37 (31%)	28 (22%)
Not given	7 (6%)	3 (2%)
Consciousness		
Normal	94 (78%)	96 (77%)
Abnormal	27 (22%)	29 (23%)
History of epilepsy		
No	76 (63%)	79 (63%)
Yes	45 (37%)	46 (37%)
Tumour pathology		
Glioblastoma	94 (78%)	97 (78%)
Anaplastic astrocytoma	16 (13%)	17 (14%)
Other	11 (9%)	11 (9%)
Main tumour location		
Frontal	43 (36%)	37 (30%)
Other	78 (64%)	88 (70%)
Tumour resection		
Total	72 (59%)	76 (61%)
Partial	43 (36%)	41 (33%)
Biopsy all types	6 (5%)	8 (6%)

30 fractions over 6 weeks. The radiation therapy doses were comparable in the two groups.

For those randomised to receive chemotherapy, 50 mg cisplatin was administered per m^2 once a week on days 1,8,15 and 22 of radiation therapy. The drug was given intravenously over 3 hours dissolved in 1 l of 0.9% NaCl. Prehydration consisted of an oral fluid intake of 2–3 l on the day before treatment, and on the treatment day of 1 l glucose 2.5% in 0.45% NaCl given over 4 h.

Of the 121 patients who received chemotherapy (Group 1) 81 were given the full dose. The mean dose to the whole of Group 1 was 80% of the scheduled dose. 125 patients received radiation therapy alone (group 2). There was no statistical difference between the two groups with respect to the distribution of the main prognostic factors (Table 1). After the completion of treatment patients were followed until the recurrence of clinical signs of tumour progression to measure the progression free interval starting at the operation day, and afterwards, until death.

Haemoglobin, total white blood cells (WBC), granulocytes, platelet counts, blood urea, creatinine, liver function (bilirubin, aspartate (GOT), alanine aminotransferase (GPT), and alkaline phosphatase) were determined weekly during therapy, and the highest toxicities were reported.

Table 2. Prognostic factors

Factors	Free interval at 6mo	12mo	24mo	P	Survival at 6mo	12mo	24mo	P
Age								
<45 yr	68*	33	22		92	60	34	
45–55 yr	58	24	10	<0.001	80	51	15	<0.001
>55 yr	44	10	3		67	32	6	
Neurological score								
1	65	31	18		91	63	31	
2	54	21	10	<0.009	75	48	15	<0.001
3	48	11	5		69	27	8	
Consciousness								
Normal	57	23	6	<0.07	81	51	19	<0.005
Abnormal	45	12	12		67	28	12	
History of epilepsy								
Yes	61	31	18	<0.003	81	56	28	<0.001
No	51	14	6		75	40	11	
Main tumour location								
Frontal	64	30	19	<0.002	86	56	31	<0.001
Other	50	16	6		73	40	11	
Pathology								
Glioblastoma	50	13	3	<0.001	75	38	8	<0.001
Other	71	48	37		87	74	49	

*Percentage.

RESULTS

Prognostic factors

Free interval and survival were closely related and similarly affected by various prognostic factors. The univariate analysis of these factors is given in Table 2. However, after multivariate analysis only pathology, normal consciousness, age and frontal location were significantly correlated with the time to recurrence and the survival. On the other hand, neither the length of history nor a total macroscopic removal correlated with outcome in this study.

Therapeutic effect

As shown by the Figs 1 and 2 the use of cisplatin did not enhance the duration of the free interval nor that of the survival

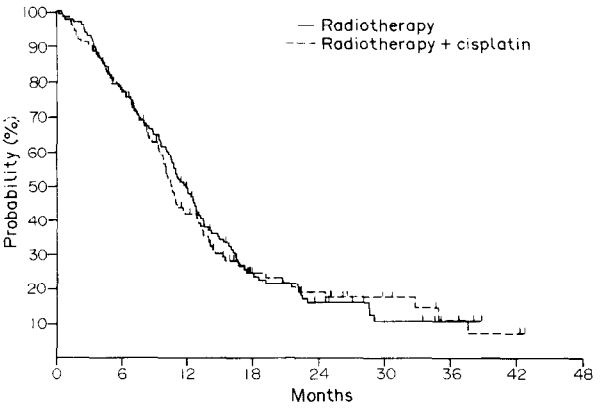

Fig. 1. Actuarial progression free survival of 121 patients treated with cisplatin plus radiation therapy, and 125 patients who received radiation therapy only.

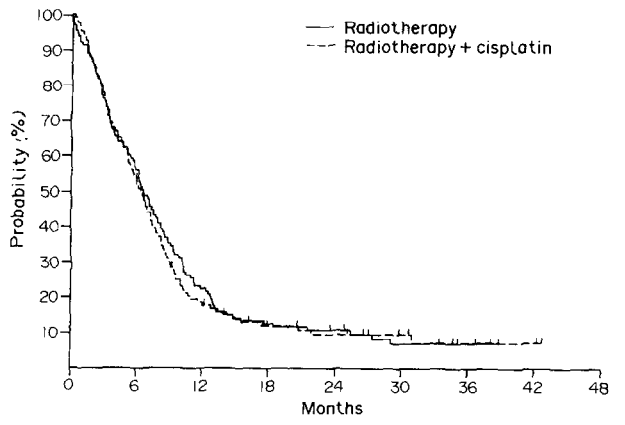

Fig. 2. Actuarial survival of 121 patients treated with cisplatin plus radiation therapy and 125 patients who received radiation therapy only.

time. The median free interval was 28 weeks for patients treated with cisplatin and 29 weeks for the control group. The corresponding figures for the survival were 46 and 52 weeks.

Drug toxicity

The toxic effects are summarised in Table 3. Nausea and vomiting was the most common side-effects, predominantly seen in the cisplatin group. These symptoms were severe (grade 4) in only 3% but milder forms (grades 2 or 3) were present in 61%.

Renal, liver and blood toxicities were rare, but slightly more common in the cisplatin arm, and reversible in all patients.

No case of clinically evident sensory neuronopathy was reported, and no patient was reported to complain of hearing loss; however, although scheduled, audiograms were not systematically performed in the majority of the patients.

There was no obvious clinical evidence of radiosensitisation as appreciated by the acute radiation induced skin reaction.

Table 3. Toxicity

Parameter	Grade (WHO scale)	Radiotherapy	Radiotherapy + cisplatin
Nausea	2*	4	24
	3	4	37
	4	0	3
Alopecia outside irradiation area		9	32
Renal function	2	1	2
Liver function	2	1	3
	3	0	2
WBC (granulocytes)	2	1 (1)	5 (7)
	3	0 (1)	1 (4)
Platelets	2	3	6
	3	1	2
	4	0	1
Haemoglobin	2	5	6
	3	3	2

*Percentage.

DISCUSSION

In the present trial the administration of cisplatin during radiation therapy has failed to increase its effect on the duration of the free interval or that of the survival time.

These negative results cannot be attributed to differences in the distribution of prognostic factors, between the treated and the control group, which could possibly occur despite random allocation of patients. Indeed the most universally [12] found prognostic factors, also found in this trial; age, pathology and neurological status were evenly distributed between the two groups, as were history of epilepsy, which has been associated with a better prognosis in several studies [12], and frontal tumour location. The latter was associated with a better outcome in some of our previous trials [10,11] and also appeared as favourable prognostic factor in the present trial.

The side-effects reported in the group of patients who received cisplatin were mild and rare, and hardly differed from these seen in patients treated with radiotherapy alone. Especially laboratory changes suggesting renal lesions, clinical symptoms or signs of ototoxicity, or sensory neuropathy were not reported. The lack of neurological side-effects is most likely related to the low doses of cisplatin used, since the earliest manifestations of peripheral neuropathy usually develop around a total dose of 300 to 350/mg/m^2 [13].

Another reason for the lack of response to cisplatin could have been the relatively low dosage of cisplatin used. Indeed the fear of enhancing cerebral edema in patients undergoing brain irradiation has limited the hydration measures, and, thereby the dose of cisplatin. However a clinical study performed by McVie *et al.* [14] using 60 mg/m^2 of cisplatin given intravenously 30 min before tumour resection, has shown tumour concentrations ranging from 3.6 to 17 ppm. As animal data indicated that concentrations of approximately 3 ppm are required to reach the radiosensitising effect of platinum, the hypothesis that the lack of effect may have been due to insufficient local concentrations of cisplatin is rather unlikely. Nevertheless, considering the way the patients tolerated the treatment higher dose could have been used. Therefore our data showing the lack of radiosensitising effect of cisplatin in patients with supratentorial malignant brain gliomas should be restricted to the relatively low doses of the drug as used in this trial.

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A Randomised Clinical Trial of Vindesine plus Cisplatin versus Mitomycin plus Vindesine and Cisplatin in Advanced Non-small Cell Lung Cancer

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This trial was carried out to evaluate the therapeutic benefit of the addition of mitomycin to vindesine plus cisplatin (80 mg/m^2) in 126 previously untreated non-small cell lung cancer (NSCLC) patients. 124 patients were evaluable for toxicity and survival and 122 for response. No patient achieved complete response. The partial response rate (PR) in the vindesine plus cisplatin (VP) and mitomycin plus vindesine and cisplatin (MVP) groups were 23% (14/62) vs. 35% (21/60) ($P = 0.13$) with a median duration of response of 23 vs. 37 weeks ($P = 0.071$), respectively. Time to progression (TTP) and survival time (ST) were similar for both treatment arms [median TTP; 14 vs. 21 weeks ($P = 0.10$), median ST; 9.1 vs. 10.5 months ($P = 0.94$), respectively]. No difference in the frequency of side-effects was observed except that WHO grade 3 and 4 leukopenia was higher in the MVP group. In multivariate analysis, the significant predictors of survival were serum albumin, sex, performance status, lactate dehydrogenase and stage. In conclusion, the addition of mitomycin to the VP regimen appears to have limited value in advanced NSCLC.
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INTRODUCTION

VERY FEW agents show activity against non-small cell lung cancer (NSCLC). Only five drugs appear to have moderate activity in NSCLC: cisplatin, ifosfamide, mitomycin, vinblastine and vindesine [1, 2]. The combination of vindesine and cisplatin has been one of the most widely used cisplatin-containing regimens for NSCLC demonstrating a reproducible response rate in the range of 30% [3–7], and a modest, but real impact on survival in patients with advanced NSCLC [8] and patients with limited disease [9] in studies comparing chemotherapy to supportive care only. However, the outcome of patients with advanced NSCLC remains poor and requires the development of more active regimens. Although there are data showing that a variety of combination chemotherapy regimens produce responses in NSCLC, it is not clear that any are associated with a significant improvement in survival [10]. Among these regimens, several combinations of mitomycin, a vinca alkaloid and cisplatin (≥75 mg/m^2) have been reported to have a reproducible response rate of at least 50% in patients with advanced NSCLC [11–14]. However, there is no clear evidence that a regimen using more than three drugs is superior to a regimen using two drugs, since the introduction of cisplatin in combination regimens in NSCLC.

In order to evaluate the potential therapeutic benefit of the addition of mitomycin to vindesine plus cisplatin, we performed a randomised trial in 126 previously untreated NSCLC patients.

PATIENTS AND METHODS

From January 1986 to March 1989 patients with histologically or cytologically proven advanced NSCLC were eligible for treatment if they had an expected survival of at least 6 weeks, measurable lesions, Eastern Cooperative Oncology Group (ECOG) performance score ≤2, white blood count (WBC) ≥ 4000/μl, platelet count ≥100 000/μl, total serum bilirubin <3 mg/dl and aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) less than twice the normal range, serum creatinine ≤ 1.5 mg/dl and creatinine clearance more than 60 ml/min. None of the patients had prior chemotherapy,

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