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A pilot study of concurrent whole-brain radiotherapy and chemotherapy combined with cisplatin, vindesine and mitomycin in non-small-cell lung cancer with brain metastasis

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Summary We have evaluated the feasibility, toxicity, and tumour response of concurrent whole-brain radiotherapy (WBRT) and chemotherapy with cisplatin, vindesine and mitomycin in the treatment of 33 patients with brain metastasis from non-small-cell lung cancer (NSCLC). The imaging response demonstrated that 25 patients (75.8%) responded to brain lesions, including five complete responders, and the response rate to primary lesion was 18%. The treatment improved at least one grade of performance status in 30% and of neurological functions in 55% of the patients. The major toxicity was leucopenia (≥ grade 3, 84.4%). Median survival was 9.7 months and the 1-year survival rate was 40%. Concurrent WBRT and chemotherapy can be safely administered to patients with brain metastasis from NSCLC, with a remarkable response rate, improvement of neurological functions and encouraging survival duration.

Keywords: whole-brain radiotherapy (WBRT); concurrent whole-brain radiotherapy and chemotherapy; cisplatin; vindesine; mitomycin; non-small-cell lung cancer

Resection of single-brain metastasis and post-operative whole-brain radiotherapy (WBRT) can improve survival compared with treatment using WBRT alone (Horton, 1971). For this reason, surgical resection has become part of the standard management of appropriately selected patients with inactive extracranial disease (Kornblith et al, 1985; Patchell et al, 1990; Vecht et al, 1993).

In most instances, brain metastases are multiple and occur in the presence of metastasis to other organs (Sundaresan et al, 1993). WBRT rather than surgery has been used as the primary treatment modality in the management of brain metastasis. More than 75% of patients benefit symptomatically from WRBT for a short time, and median survival varies from 15 to 18 weeks (Lee et al, 1989).

As most patients have disseminated disease, more attention should be paid to the use of systemic chemotherapy in brain metastases, which could offer control of cranial as well as extracranial disease. Chemotherapy for brain metastases has been considered ineffective because the drugs do not penetrate the intact blood–brain barrier (BBB). However, some reports have demonstrated a breakdown of the BBB in metastatic brain tumours, which diminishes the restrictions in the transport of drugs normally exerted (Workman, 1986; Greig, 1989). Several studies have reported a higher concentration of drugs in brain tumours than in the brain or an increased tumour–plasma ratio (Stewart et al, 1979, 1983, 1984).

The mitomycin, vindesine and cisplatin (MVP) regimen has demonstrated neurological improvement and good response in patients with brain metastasis from NSCLC in Japan (Kasamatsu et al, 1990; Yamamoto and Furuse et al, 1995).

The combination of chemotherapy and radiotherapy could increase cytotoxicity by interfering with cells' ability to repair injury caused by the other treatment. In this manner, combined treatments could result in additive or supra-additive cytotoxic effects. Also, there are laboratory data to suggest that cisplatin increases radiation sensitivity (Kornblith et al, 1985).

The objective of this study is to evaluate the technical feasibility, toxicity and tumour response of concurrent WBRT and MVP in the treatment of patients with brain metastasis from NSCLC.

PATIENTS AND METHODS

Eligibility

Patients had to fulfil all the following criteria to be entered in the study: a histologically or cytologically proven diagnosis of NSCLC; stage IV with brain metastasis; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 3; age less than 75 years; no massive pleural effusion; no severe pain due to bone metastasis; adequate haematological [Hb ≥ 9.5 g dl^{-1}, white blood cell count ≥ 4000 μl^{-1}, platelet (PLT) count ≥ 100 000 μl^{-1}], hepatic (serum bilirubin ≤ 2.0 mg dl^{-1}; ALT, AST and alkaline phosphatase ≤ double upper limit of normal) and renal (serum creatinine ≤ 1.1 mg dl^{-1}) functions; no active concomitant malignancies; no previous treatment of primary or brain lesion; and no consciousness disturbance or systemic convulsion. Informed consent was obtained from all patients.

Treatment

Chemotherapy consisted of vindesine (3 mg m^{-2} on days 1, 8, 29 and 39), cisplatin (100 mg m^{-2} on days 1 and 29) and mitomycin

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Table 1 Neurological function classification

1. Able to work or to perform normal activities: neurological finding minor or absent
2. Able to carry out normal activities with minimal difficulties. Neurological impairment does not require nursing care or hospitalization
3. Seriously limited in performing normal activities. Requiring nursing care or hospitalization. Patients confined to bed or wheelchair or have significant intellectual impairment
4. Unable to perform even minimal normal activities. Requiring hospitalization and constant nursing care and feeding. Patients unable to communicate or in coma

Criteria are from Borgelt et al (1980).

Table 2 Survival of all patients (n = 33)

Variable	Estimated median survival (days)	95% Confidence interval (days)	P-value (log-rank test)
Median age 62 years (range 39–73)			
<65 years (20)[a]	311	132–449	0.7131
≥65 years (13)	290	133–409	
Sex			
Male (16)	187	104–366	0.0689
Female (17)	409	191–117	
PS			
0–1(1+13)	311	191–117	0.8352
2–3(11+8)	210	117–449	
Histology			
Adenocarcinoma large cell (26+4)	299	144–449	0.3588
Squamous cell (4)	284	72–404	
Brain symptoms			
Yes (23)	311	133–449	0.7321
No (10)	234	191–455	
Brain lesion			
Single (19)	366	291–492	0.0288
Multiple (14)	163	85–378	
Other metastatic lesion			
Yes (23)	210	132–404	0.0795
No (10)	378	290–660	
FN			
0–1 (17)	299	210–409	0.8024
2–4 (16)	164	117–449	

[a]Numbers in parentheses are numbers of patients.

(8 mg m^{-2} on days 1 and 29). The doses were modified on the basis of blood counts and renal functions on the day of therapy (Furuse et al, 1995).

On day 2 of chemotherapy, WBRT was administered using a linear accelerator for 5 weeks at a dose of 2 Gy given 20 times. The dose was given in five fractions per week.

Response

Treatment response was evaluated through periodic reassessment of PS and neurological function (FN) as described by Borgelt (1980) and the Radiation Therapy Oncology Group (Table 1). Patients were evaluated before treatment–weekly for the first 4 weeks, monthly for 2 or more months and every 3 months thereafter.

Response to brain lesions was evaluated by contrast-enhanced brain computerized tomography (CT) before treatment and 8 weeks after treatment. If the findings showed partial or complete response after WBRT, these responses were reconfirmed after 4 weeks. If neurological symptoms occurred after WBRT, brain CT was again performed. The responses of brain metastastic lesion and primary tumours were evaluated according to the World Health Organization (WHO) criteria (1979).

The duration of response was measured from the first day of treatment with concurrent WBRT and chemotherapy. Brain failure was defined as recurrence of tumour anywhere in the brain. The survival was calculated on the basis of the period from the start of the treatment to death or the last follow-up.

Toxicity

Patients were evaluated every week during WBRT and chemotherapy. Toxicity was rated according to WHO criteria (1979).

Statistical methods

Survival was calculated on the basis of the period from the start of treatment to death or the last follow-up. The survival curve was calculated by the method of Kaplan and Meier.

Available treatment variables, which in some other series proved to have influence on the treatment of NSCLC, were investigated for any possible relationship to the probability of survival as a result of the treatment of NSCLC, first in univariate analysis and subsequently by application of a multiple regression model. The univariate was based on 2 × 2 tables, and differences were tested by use of the chi-square test. A P-value of 0.05 was regarded as significant.

Differences in survival duration were compared using a two-sided log-rank test (Mantel, 1966). To adjust for any confounding variables and to assess the relative importance of different prognostic variables for survival, Cox's proportional hazards model (1972) was used.

RESULTS

Distribution of prognostic factors

From April 1991 to August 1994, 33 patients were entered into this study. The distribution of the patients' prognostic factors is given in Table 2. The estimated median survival of all patients from the start of treatment to death or the last follow-up was 229 days, with 30% being alive 1 year after treatment (Figure 1). The effects of a number of potential prognostic factors on survival was examined initially using univariate analysis (Table 1). Patients with a single metastatic lesion survived longer than those with multiple lesions (P = 0.0288). Other prognostic factors had no significant effect on survival.

Stepwise multiple regression analysis was carried out to determine the prognostic factors, except for histology, significantly influencing survival. The only statistically significant prognostic factor found to be associated with survival was the number of brain metastatic lesions (P = 0.0339).

Toxicity

In total, 63 courses of MVP were given. Twenty-six patients received two courses, three patients three courses and five only one course. The toxicities observed during the entire treatment of 33 patients are listed in Table 3. The main toxicity was myelosuppression, in particular leucopenia. Of the 33 patients, 28 (84.8%)

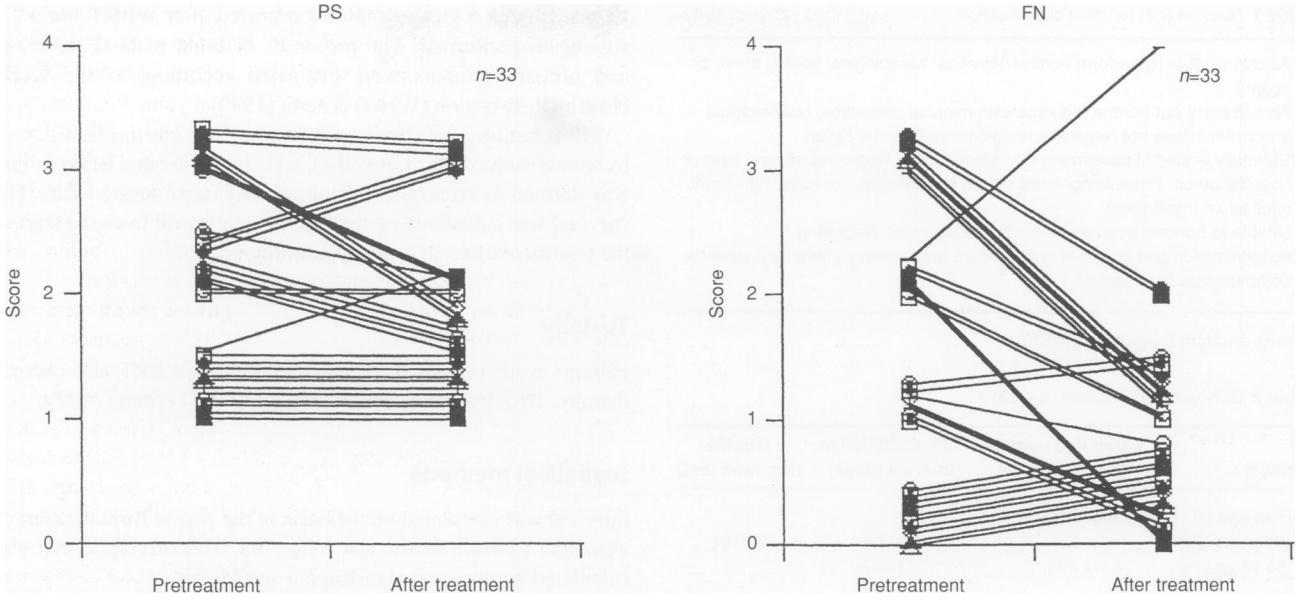

Figure 1 Changes of scores in PS and FN after WBRT and MVP

Table 3 Toxicity in 33 patients

Toxicity	WHO				No. of toxicities ≥ grade 3(%)
	1	2	3	4	
Leucopenia	0	5	19	9	84.8
Thrombocytopenia	5	7	5	3	24.2
Anaemia	5	13	7	1	3.0
Nausea/vomiting	11	16	1	0	0
Neutropenic fever	0	2	0	0	0
Infection	4	3	0	0	0
Elevation of serum creatinine	8	2	2	0	6.0
Elevation of transaminases	2	0	0	0	0
Elevation of alkaline phosphatase	2	0	0	0	0

Table 4 Response to treatment

	No. of patients	Response (%)					Total response rate(%)
		CR	PR	NC	PD	NE	
Brain metastases							
Overall	33	5(15)	20 (61)	7	0	1	75.8[a]
Solitary lesion	19	4 (21)	10 (53)	5	0	0	73.7
Multiple lesions	14	1 (4)	10 (42)	2	0	1	45.8
Primary tumour	33	0	6 (18)	22	0	5	18.2

[a]95% Confidence interval 57.74–88.90%. CR, Complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not eligible. Numbers in parentheses are percentages.

experienced grade 3 or 4 leucopenia. Grade 3 or 4 thrombocytopenia was observed in eight patients (24.2%). Grade 3 anaemia was observed in one patient (3%). Thirty-three per cent of the patients experienced grade 1 nausea and vomiting, 48% grade 2 and 3% grade 3. We did not experience treatment-related death or toxicity of the central nervous system as a result of WBRT and MVP.

Response

The total response rate for brain lesions in these 33 patients was 75.8% as shown in Table 4 (five complete responses (CR) and 20 partial responses (PR), 95% confidence interval 57.74–88.90%). One patient was not assessable. Of the 25 patients who had a CR or PR after WBRT and MVP, five patients had local brain recurrence with neurological symptoms at 129, 226, 321, 576 and 877 days

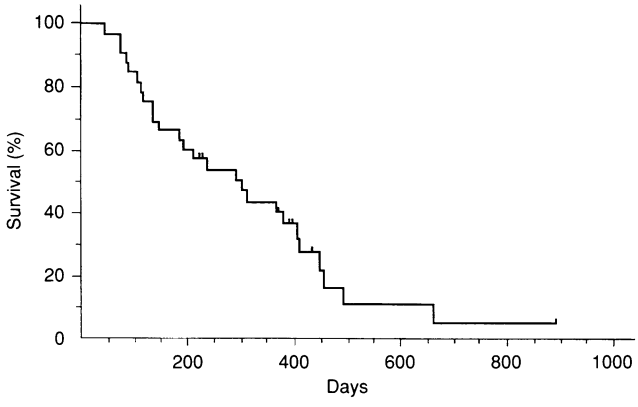

Figure 2 Overall survival of 33 eligible patients treated with WBRT and MVP

after the treatment. The median duration of response for brain lesions was 223 days (range 43–892 days). In 33 primary lung cancers, six (18%) had a PR after WBRT and MVP.

Performance status and neurological function

Evaluation of performance status and neurological function according to response is shown in Figure 1. Among the 33 patients, ten (30%) improved in more than one category of PS, and 18 (54.5%) improved in more than one score of FN. However, among the 33 patients, six (18%) worsened in at least one category of PS and two (6%) worsened in at least one score of FN. At the median follow-up of 8.0 months (range 1.4–29.7 months), five patients (15%) had died of local recurrence of brain lesions. Of the 23 patients who had neurological dysfunction before the treatment, 14 had (61%) died of their other metastatic lesions before recurrences of brain lesions, three had died of local recurrence of brain lesions and six were alive.

Survival

At the median follow-up time of 8.0 months (range 1.4–29.7 months), the median survival time in these 33 patients was 8 months and the 1-year survival rate was 40% (Figure 2). Of these 33 patients, 26 died because of cancer and seven remained alive 7.4, 12.3, 13.2, 13.3, 14.5, 14.9 and 29.7 months after the treatment. Of these 26 patients, 21 had no local brain recurrence.

DISCUSSION

Two large studies of the Radiation Therapy Oncology Group (Lee et al, 1989) demonstrated that more than 75% of patients benefited symptomatically from WBRT for a short time, but median survival varied from 15 to 18 weeks. Brain metastasis as a cause of death was reported in 31–49% of patients. Thus, in spite of WBRT, up to half of the patients eventually developed recurrence of their brain lesions before death due to other metastases.

Recent reports on chemotherapy for patients with brain metastases from small-cell lung cancer (Kristjansen and Hansen, 1988; Lee et al, 1989; Twelves et al, 1990; Postmus et al, 1995), adenocarcinoma of the lung (Kantarjian et al, 1984), gestational choriocarcinoma (Weed and Hammond, 1980; Sen et al, 1987), germ cell malignancies (Newlands, 1985; Allen et al, 1987) and breast cancer (Boogerd et al, 1992) describe response rates in the brain similar to those in other organ sites. Kasamatsu et al (1990) in Japan reported on a study in which five patients with NSCLC and brain metastases were treated with a mitomycin, vindesine and cisplatin regimen. Of the five patients, three had a PR for brain lesion and five showed neurological improvement. Their survival time ranged from 6 to 8 months. Also, Yamamoto et al (1993) reported that 22 NSCLC patients associated with brain metastasis were treated with chemotherapy regimens including cisplatin, with three patients having a CR and two a PR for brain lesions.

In patients with malignant gliomas, adjuvant chemotherapy in addition to WBRT increased the number of long-term survivors (Walker et al, 1978). Hidalgo et al (1987) reported, in his series, that five patients with NSCLC and brain metastases were treated with weekly cisplatin (40–60 mg m^{-2}) during WBRT (50 Gy over 5 weeks). Three patients had a CR and two a PR to the treatment, and four were alive more than 6 months later. Also, Lange et al (1987) reported that 27 patients with NSCLC and brain metastases were treated with ifsofamide (daily for 5 days at 2 g m^{-2}) and BCNU (at 30 mg m^{-2} on days 1,3 and 5) and radiotherapy was given simultaneously. Of the 27, seven patients had a CR and 12 a PR. The mean time of survival was 9.5 months for patients with NSCLC. In an uncontrolled study of patients with brain metastases from solid tumours, concurrent radiotherapy and chemotherapy appeared to increase the median survival, although no information was provided regarding the extent of extracranial metastatic disease or other prognostic factors.

In our study of concurrent WBRT and chemotherapy with cisplatin, vindesine and mitomycin for NSCLC with brain metastasis, the response rate of the brain lesion to treatment was 75.8% (including five patients with CRs), and the response rate of the primary lesion to treatment was 18%. Also, the treatment improved at least one grade of performance status in 30% and at least one grade of neurological functions in approximately 55% of the patients. Median survival was 8 months and the 1-year survival rate was 40%. Median survival duration and 1-year survival rate, in our study, were better than the median survival durations (3–6 months) and 1-year survival rates (approximately 20%) in the previously mentioned WBRT-alone trials (Chu and Hilaris, 1961; Order et al, 1968; West and Maor, 1980), although our study was uncontrolled and had a bias for patient selection.

The major toxicity in this pilot study was leucopenia. Late toxicity of concurrent WBRT and chemotherapy are becoming more important with the longer survival of patients with metastatic disease (DeAngelis et al, 1989). It may be because of the short duration of survival in our series that we have experienced no neurotoxicity. Brain metastasis was the only clinical site of symptoms in 15% of the patients in our study. Thus, in spite of concurrent radiotherapy and chemotherapy, up to two-thirds of the patients died of recurrence of their other lesions before recurrence of brain lesions.

We have shown the ability to safely administer concurrent WBRT and MVP chemotherapy for patients with NSCLC and brain metastasis. There is an excellent imaging response rate to brain tumours, associated with improvement of neurological function and notable survival rates at a median survival duration and at 1 year after treatment. To evaluate the true benefit and the best use (accounting for quality of life and toxicity) of this treatment modality, we are conducting a prospective multicentre randomized study comparing WBRT with or without concurrent chemotherapy for patients with NSCLC and brain metastasis.

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