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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

Tetsu Shinkai, Kenji Eguchi, Yasutsuna Sasaki, Tomohide Tamura, Yuichiro Ohe, Akira Kojima, Fumihiro Oshita and Nagahiro Saijo

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,

Correspondence to T. Shinkai.
The authors are at the Department of Medical Oncology, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104, Japan.
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radiotherapy or surgery. Written informed consent was obtained in every case. Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses, chest roentgenogram, electrocardiogram and urinalysis. All patients underwent radionuclide bone scan, computed tomography of the brain and thorax and ultrasonography or computed tomography of the abdomen. Physical examination, complete blood counts and chest roentgenograms were obtained weekly for the first 8 weeks of treatment and every 2–4 weeks thereafter. Tests of measurable disease parameters except chest roentgenogram were repeated at 4 weeks from initiation of chemotherapy and every 6 weeks thereafter. Biochemical tests and serum electrolytes were repeated at 1–2 week intervals. Disease was defined as limited if the tumour was confined to one hemithorax, including mediastinal or supraclavicular nodes. Disease beyond these confines was classified as extensive.

Patients were randomly assigned to receive vindesine plus cisplatin (VP) or mitomycin plus vindesine plus cisplatin (MVP). Randomisation was carried out by the sealed card method. No stratification parameters were used in the randomisation process. In the VP regimen, vindesine 3 mg/m^2 was given by rapid intravenous injection once a week for the first 5 weeks and then on a schedule of every 2 weeks. Cisplatin at a dose of 80 mg/m^2 was given intravenously on days 1, 22 and 43 and every 6 weeks thereafter. In the MVP regimen, mitomycin 8 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 were given 3 times every 4 weeks, then every 6 weeks. In both arms, cisplatin was administered intravenously over 20 minutes after intravenous prehydration with 1 l of 5% glucose in 0.45% NaCl. Following the administration of cisplatin, patients received intravenous mannitol (20%) at a rate of 50 ml/h over 6 h and 2000 ml of 5% glucose in 0.45% NaCl with 20 mmol/l K^+ at a rate of 200 ml/h. The mannitol-induced diuresis was similar to that of Hayes *et al.* [15]. To control cisplatin-induced emesis, patients received high-dose metoclopramide (2 mg/kg intravenously every 2 h × 4) plus intravenous dexamethasone and promethazine.

In both arms, subsequent cycles of cisplatin were given if the WBC was ≥3000/μl, the platelet count ≥75 000/μl and serum creatinine <2.0 mg/dl. Vindesine and mitomycin were withheld until recovery of the counts if the leucocyte and/or platelet count fell below these levels. No dosage modification was made based on nadir count. Cisplatin was delayed for an additional week if the serum creatinine was ≥2.0 mg/dl and it was discontinued if serum creatinine did not decrease below 2.0 mg/dl.

In the case of stable disease or no response at 3 doses of cisplatin and 6 doses of vindesine in the VP arm and three courses in the MVP arm, the treatment was discontinued. In responding patients, chemotherapy was continued until there was evidence of progressive disease or unacceptable toxicity. Radiation could be given to treat documented brain metastasis or symptomatic bone lesions. Central nervous system (CNS) metastasis was present at the time of diagnosis in 9 patients (8 in the VP arm, 1 in the MVP arm). None of these patients had symptoms or signs referable to the brain tumour, and CNS metastasis was detected by computed tomography of the brain in a pretreatment staging procedure. These 9 patients received therapeutic whole brain irradiation (32–40 Gy in 16–20 fractions over 4 weeks) immediately prior to the initiation of chemotherapy.

To be eligible, all patients had to have measurable lesions on chest roentgenogram or physical examination. Clearly definable lesions observed by computed tomography or ultrasonography of the liver or abdomen were acceptable. Pleural effusion, clinical hepatomegaly and radionuclide scans were not acceptable criteria for measurable disease. The criteria for response was as follows. Complete response was defined as the complete disappearance of all evidence of tumour for at least 4 weeks. Partial response was defined as at least a 50% reduction of the sum of the product of the two greatest perpendicular diameters of all indicator lesions for at least 4 weeks and without the appearance of new lesions or progression of any lesions. Disease progression was defined as at least a 25% increase in tumour area or the appearance of new lesions. All other circumstances were classified as stable disease. Patients with early toxic death due to chemotherapy were considered as evaluable for response.

Pretreatment prognostic factors analysed included age, sex, ECOG performance status, weight loss for the last 6 months, histology, stage of disease, extent of disease, distant metastatic sites at presentation (central nervous system, liver and bone), number of metastatic sites, carcinomatous hereditary tendency, total lymphocyte count, serum albumin, serum cholesterol, alkaline phosphatase, lactate dehydrogenase (LDH), serum carcinoembryonic antigen and treatment assigned.

The duration of overall response and survival were recorded from the first day of treatment [16]. Survival curves were calculated by the method of Kaplan and Meier [17]. Tests of difference in survival distribution, time to progression and response duration were based on a generalised Wilcoxon–Gehan test [18] and log rank test [19]. The χ^2 test was used to test for differences in response rate and toxicity. The Cox proportional hazards model [20] was performed for a multivariate analysis of prognostic variables. Differences yielding observed significance levels of 5% or above were not considered statistically significant.

This trial was designed to detect a 50% increase in the median survival in the group of patients treated with MVP compared with VP ($\alpha = 0.05$, $\beta = 0.2$, i.e. a power of 80%) [21]. Our reason for specifying in the design phase a difference of this magnitude was our interest in only identifying new treatment regimen that had a biologically meaningful impact on significantly prolonging survival.

RESULTS

A total of 126 patients were registered between January 1986 and March 1989, but 2 (1.6%) were ineligible for the study (1 in the VP arm and 1 in the MVP arm) for the following reasons: no NSCLC histology (1) and candidate for surgery (1). Among the 124 patients evaluable for survival, 2 (1.6%) were not evaluable for response [1 each in the VP and MVP arms, lost to follow-up (1), refused therapy (1)]. Thus, 122 patients were evaluable for response.

The characteristics of the eligible patients are summarised in Table 1. There was no significant imbalance between the two treatment groups, although there was an imbalance in patients with brain metastasis ($P = 0.018$). ECOG performance status was 0–1 in 111 patients (90%) and 80 patients had stage IV [22] and 31 had metastasis to 2 organs or more. The majority of the patients had adenocarcinoma (70%).

As shown in Table 2, no patient achieved complete response. Among the 63 patients treated with VP, there were 14 partial responders (23%; [95% confidence interval (95% CI), 14–34%]). 21 of 61 patients treated with MVP had a partial response (35%; [24–48%]). The difference was not statistically significant ($P = 0.13$). The response rates to VP and to MVP in patients with limited disease were 26% (6/23) and 50% (15/30), respect-

Table 1. Patients' characteristics

Characteristics	Vindesine/ cisplatin	Mitomycin/ vindesine/ cisplatin
Total patients	63	61
Age (years)		
Median (range)	58 (36–75)	60 (27–74)
Sex		
Male	45 (71)	45 (74)
Female	18 (29)	16 (26)
ECOG performance status		
0	9 (14)	10 (16)
1	45 (71)	47 (77)
2	9 (14)	4 (7)
Weight loss (≥10% body weight)		
Yes	12 (19)	8 (13)
No	47 (75)	47 (77)
Unknown	4 (6)	6 (10)
Histology		
Adenocarcinoma	43 (68)	44 (72)
Squamous cell ca.	8 (13)	11 (18)
Large cell ca.	8 (13)	5 (8)
Adenosquamous ca.	3 (5)	1 (2)
Undifferentiated	1 (2)	0
Stage		
IIIA	6 (10)	9 (15)
IIIB	14 (22)	15 (24)
IV	43 (68)	37 (61)
Site of metastases		
Brain	8 (13)	1 (2)*
Liver	2 (3)	5 (8)
Bone	17 (27)	20 (33)
Adrenal	2 (3)	1 (2)
Distal lymph nodes	3 (5)	5 (8)
No. of metastatic sites		
0	20 (32)	24 (39)
1	27 (43)	22 (36)
≥2	16 (25)	15 (25)

Unless otherwise specified, values = no. of patients (%); ca. = carcinoma.
*P = 0.018.

Table 2. Therapeutic responses

	Vindesine/ cisplatin	Mitomycin/ vindesine/ cisplatin
Total patients	63	61
Complete response	0	0
Partial response	14	21
Stable disease	28	25
Disease progression	19	13
Early death	1	1
Inevaluable	1	1
Response rate	22.6% (14/62)	35.0% (21/60)
95% confidence limits	14.0–34.4%	24.2–47.6%

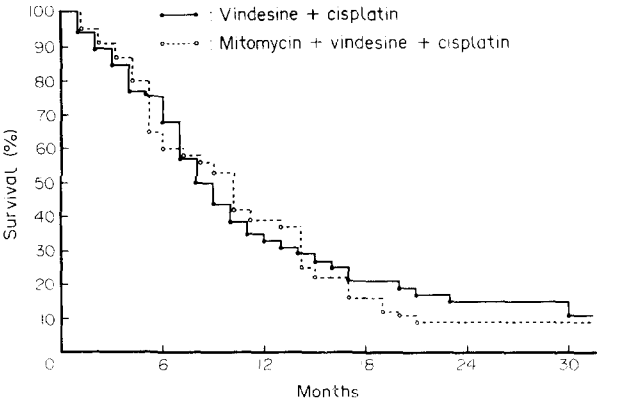

Fig. 1. Actuarial survival curves of patients according to regimen adjusted for brain metastasis.

ively. This difference was also not significant (P = 0.08). In patients with extensive disease, the response rate was 21% (8/39) and 20% (6/30) for patients treated with VP and MVP, respectively (P = 0.95).

The median duration of overall response was 23 weeks and 37 weeks for patients treated with VP and MVP, respectively. This difference was not statistically significant (P = 0.07). Time to progression (TTP) was also not different between the two groups (median TTP; 14 weeks vs. 21 weeks, respectively, P = 0.10). 23 patients (36%) treated with VP and 18 patients (30%) treated with MVP who had limited disease that could be encompassed within one radiation therapy port received radiotherapy (50–60 Gy in 25–30 fractions for 5–6 weeks) for local progression after chemotherapy.

The overall survival was not significantly different between the two treatment groups (P = 0.94). The median survival times for the patients treated with VP and for those treated with MVP were 9.1 months and 10.5 months, respectively. 7 patients were alive in the MVP treatment and 8 patients in the VP treatment arm. Analysis of those patients with limited disease showed a median survival of 10.8 months for the MVP arm and 12.6 months for the VP arm (P = 0.62). In patients with extensive disease, a median survival was 7.8 months for the MVP arm and 7.7 months for the VP arm (P = 0.78). There was an imbalance in patients with brain metastasis between the two arms (Table 1); however, there was no significant difference in survival adjusted for brain metastasis as shown in Fig. 1 (P = 0.70) (median survival time; 10.1 months for the MVP arm and 8.8 months for the VP arm).

In respect of an analysis of the factors related to survival, univariate analysis disclosed a significant prognostic influence for sex, performance status, prior weight loss, stage, disease extent, CNS metastasis, liver metastasis, bone metastasis, number of metastatic sites, serum albumin, serum cholesterol and LDH. The 12 factors (sex, performance status, prior weight loss, stage, disease extent, CNS metastasis, liver metastasis, bone metastasis, number of metastatic sites, serum albumin, serum cholesterol and LDH) were used in a stepwise Cox proportional hazard model to identify pretreatment factors that may have had a significant influence on survival. In the multivariate regression analyses, a normal value of serum albumin, female sex, good performance status, a normal LDH and limited stage were favourable prognostic factors. A logistic regression analysis [23] for prediction of response showed that there were no significant prognostic factors for response. When

Table 3. Toxicity

	VP (n = 63)			MVP (n = 61)		
WHO grade	2	3	4	2	3	4
Leukopenia*	19	27	4	11	34	9
Thrombocytopenia	3	2	0	5	6	1
Anaemia	25	10	0	23	15	0
Haemorrhage	0	0	0	0	0	1
Infection	2	0	1	4	0	0
Nausea and vomiting	25	7	0	26	11	0
Diarrhoea	0	0	0	1	0	0
Transaminases (SGOT/SGPT)	3	2	1	1	1	1
Renal dysfunction	1	1	0	2	1	0
Alopaecia	23	6	0	32	8	0
Peripheral neurotoxicity	10	0	0	10	0	0
Hearing disorder†	4	5	0	2	4	0

*P = 0.016 (grades 3, 4). All others not significant.
†Eastern Cooperative Oncology Group toxicity criteria.

the survival curve was adjusted for serum albumin, performance status, sex, LDH and stage there was still no difference between the 2 arms (P = 0.79) (median survival times: 9.8 months for the MVP arm and 7.8 months for the VP arm).

Toxicity was acceptable. In regard to the haematological toxicity encountered during the first 12 weeks of treatment, leukopenia was the most common manifestation of marrow toxicity as shown in Table 3. WHO grade 3 and 4 [16] leukopenia was more frequently observed in patients treated with MVP (70%, 43/61) than in patients treated with VP (49%, 31/63) (P = 0.016). No significant difference between the two treatment groups could be observed for thrombocytopenia or anaemia. There were 2 treatment-related deaths. 1 patient on the VP arm died of sepsis during a period of drug-induced leukopenia after the first course of chemotherapy and 1 on the MVP arm died of bleeding in the abdomen during a period of drug-induced thrombocytopenia after the first course of chemotherapy. No relationship between the treatment arms and the frequency of non-haematological toxic effects was observed. 5 patients in each treatment group had cisplatin discontinued because of persistent serum creatinine elevation. No cases of haemolytic-uraemic syndrome were recorded. The majority of patients experienced some degree of nausea, vomiting and alopaecia. No respiratory syndrome compatible with mitomycin-induced pulmonary toxicity was encountered. A comparison was made between the two groups with respect to changes from the baseline in performance status and weight 8–12 weeks after the start of treatment (3–4 weeks after the latest administration of cisplatin). There were no significant differences between the two groups with respect to changes in performance status and weight.

In patients treated with VP, the median total doses of vindesine and cisplatin per patient were 12 mg/m^2 (range, 3–54) and 160 mg/m^2 (range, 80–640), respectively. In patients treated with MVP, the median total doses of mitomycin, vindesine and cisplatin per patient were 24 mg/m^2 (range, 8–56), 15 mg/m^2 (range, 6–42) and 240 mg/m^2 (range, 80–560), respectively.

DISCUSSION

The current study was designed to determine the therapeutic benefit of adding mitomycin to vindesine plus cisplatin in previously untreated advanced NSCLC. The survival outcome for NSCLC patients is bleak. Thus, this trial was designed to detect a 50% increase in the median survival time in the patients treated with MVP. This design specification was based on our interest in identifying new treatments that markedly prolonged survival, due to the current state of treatment for patients with this disease. We closed the study at the time 126 patients (83% of the sample size required [21]) had entered this study. The time of analysis was selected because interim analyses of our data were conducted periodically, with roughly 80% of projected study accrual representing an anticipated interim evaluation point. Stopping the study early was decided for the following reason: the analysis of overall survival and survival adjusted for prognostic factors after 126 patients had been entered showed that the survival curves were very similar for both treatment groups as shown in Fig. 1 (median survival time 10.5 months vs. 9.1 months). Moreover, with these observed survival data and with 83% of the projected accrual completed, the probability of obtaining a significant difference in favour of MVP after accruing the remaining 17% of patients on study was very low (<5%). The statistical calculations that led us to this conclusion are known as conditional power calculations [24], which indicate the power to detect a marked difference conditional on the results obtained so far. Thus, because it was most unlikely that our study conclusions would change, we chose to stop the study at this time. In addition, although the response rate comparison was not the primary end point of the current study, the response rate to MVP was 35% and 23% for VP. The difference in response rate between the two regimens was only 12% and a total of 250 patients would have been required (with respective α and β errors of 0.05 and 0.2) in order to detect a significant difference in the response rate [25].

With the introduction of cisplatin-based chemotherapy, the issue of cisplatin dose intensity must be addressed [26]. In NSCLC, a randomised study comparing two doses of cisplatin (120 mg/m^2 vs. 60 mg/m^2) combined with a fixed dose of vindesine resulted in a significantly longer response duration and survival in responding patients receiving higher dose (120 mg/m^2) of cisplatin [3]. Gandara *et al.* [27] reported that high-dose cisplatin on a divided schedule (100 mg/m^2 on day 1 and 8) produced a 36% response rate with a median survival of 37 weeks as a single agent. Several ECOG trials failed to demonstrate a major impact of cisplatin dose [6] and the EORTC failed to show a benefit by increasing the dosage of cisplatin in combination with etoposide in advanced NSCLC [28]. Although the dose intensity of cisplatin may be important factors in achieving optimal results, we have chosen to use a modest dose of cisplatin (80 mg/m^2) in the present study. In our previous randomised trial to evaluate whether a higher dose (120 mg/m^2) of cisplatin might improve survival, we compared cisplatin at 120 mg/m^2 and 80 mg/m^2 in combination with vindesine. The high-dose regimen of cisplatin did not result in a significantly better response rate or survival advantage and was associated with greater toxicity, especially nephrotoxicity [29]. The response rate for VP was 23% in this study, lower than the 43% response rate observed in a previous trial [5]. However, the 95% confidence interval for the difference between these two observed percentages includes 0. This indicates that the difference in objective response rates between these two studies is not significantly different at the P = 0.05 level.

This study failed to demonstrate the superiority of MVP over VP in advanced NSCLC. Two previous randomised trials comparing MVP and other combination regimens as well as single agents also failed to demonstrate sufficient therapeutic benefit for MVP [6, 30, 31]. It is clear that the duration of mitomycin therapy may also impact outcome with longer duration of such therapy associated with poor outcome [32]. Research in NSCLC has been made difficult by the lack of effective drugs. The evaluation of promising phase II drugs as initial chemotherapy would seem important, as advances in this disease will only be made by the discovery of more active single agents and the successful inclusion of such drugs into more logical and rational combination chemotherapy regimens.

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