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The benefit of cisplatin-based polychemotherapy for adenocarcinoma of the lung

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Summary. We studied the efficacy of cisplatin-based polychemotherapy for adenocarcinoma of the lung. A total of 136 patients were randomized for treatment with either cyclophosphamide, Adriamycin, cisplatin and mitomycin C (CAPM) or mitomycin C, cytosine arabinoside and tegafur (MCT). Radiation was given to the chests of patients at stage III. The differences in the response rate (35% in the CAPM arm and 13% in the MCT arm) were statistically significant (P <0.01). However, the significant difference was observed in stage-IV patients (CAPM, 33%; MCT, 4%; P <0.001) and not in stage-III patients (CAPM, 40%; MCT, 40%). The median period of survival was 9.5 months for the CAPM arm and 5.5 months for the MCT arm (P <0.035, Wilcoxon-Gehan test; P <0.1, log-rank test). Improved median survival for the CAPM regimen was demonstrated only by stage-IV patients (CAPM, 10 months; MCT, 5.5 months; P <0.025, Wilcoxon-Gehan test; P <0.05, log-rank test). The duration of the response, including PRs and NCs, was significantly different depending on the treatment, showing 5 months for the CAPM arm and 3 months for the MCT arm (P <0.05). The significant difference was also only observed in stage-IV patients. Myelosuppression was more severe with CAPM than with the MCT regimen. Nausea and vomiting were significantly increased in patients receiving the CAPM regimen. However, all toxicities were acceptable and there were no treatment-related deaths. We concluded that cisplatin-based chemotherapy, CAPM therapy, was of more benefit to patients with adenocarcinoma of the lung than MCT therapy.

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Introduction

Non-small-cell carcinoma of the lung (NSCLC) is traditionally one of the malignancies most resistant to chemotherapy. However, the introduction of cisplatin-based combination chemotherapy to fight NSCLC has led to significant advances in therapy for this disease. Recently, a response rate of 30%–50% has become routine. However, the median survival of patients remains only 6–12 months, despite the application of intensive combination chemotherapy [5, 7, 10, 11]. In addition, chemotherapy is more intensive, and the toxicity is more severe, thereby affecting the quality of life [12]. In consideration of the toxicity and survival rates reported in previous studies, it is important to clarify whether intensive chemotherapy, especially cisplatin-based chemotherapy, is really worthwhile in treating NSCLC. We designed a prospective study in which patients were randomly allocated to either mild chemotherapy (MCT) or a cisplatin-based polychemotherapy regimen (CAPM) for unresectable adenocarcinoma of the lung.

Materials and methods

From July 1983 to June 1985, 136 patients with histologically proven adenocarcinoma of the lung underwent this randomized study. The patients were required to have measurable or evaluable lesions on physical examination or a chest roentgenogram, to have received no prior chemotherapy or radiotherapy, to be no older than 75 years of age, to have an ECOG (Eastern Cooperative Oncology Group) performance status (PS) of <3, and to demonstrate good renal (serum creatinine, <1.5 mg/dl) and hematologic (WBC count, $\geq$4,000/mm^3; platelet count, $\geq 10 \times 10^4$/mm^3) functions.

The pretreatment evaluation consisted of a medical history and physical examination, a chest X-p film with tomography, a computerize tomographic (CT) scan, fiberoptic bronchoscopy, bone scintigraphy, a liver CT scan or echography, evaluation of the blood chemistries, electrolytes and serum creatinine, and liver function tests. The follow-up studies included weekly physical examinations and a complete blood count for the subsequent 8 weeks of treatment; thereafter, these studies were repeated biweekly. Biochemical tests, evaluations of serum electrolytes and serum creatinine, and chest roentogenograms were repeated monthly.

Table 1. Patient characteristics

	CAPM	MCT
Patients (*n*)	69	67
Sex (M/F)	43/26	44/23
Age:		
Median	60 years	63 years
Range	27–75 years	37–75 years
Disease stage:		
III	18	18
IV	51	49
Performance status:		
0	9	5
1	37	36
2	13	17
3	10	9

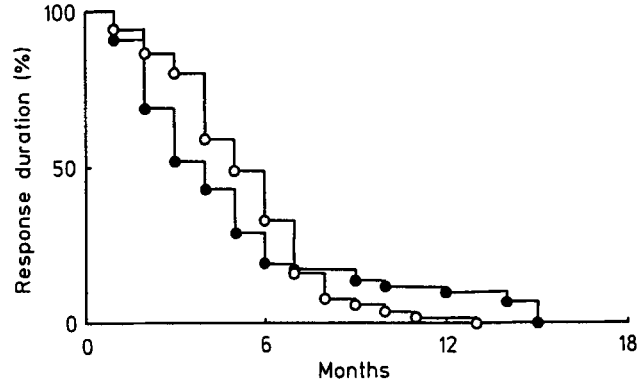

Fig. 1. Response duration for patients treated with the CAPM and MCT regimens. ○, CAPM ($n = 49$); ●, MCT ($n = 42$). $P < 0.05$ according to the Wilcoxon-Gehan test; $P < 0.8$ according to the log-rank test

The patients were divided at the time of registration into those with stage III and those with stage IV disease, according to the criteria set by the American Joint Commission on Staging [2], and then randomized to receive the CAPM or MCT regimen. The CAPM regimen consisted of 400 mg/m² i.v. cyclophosphamide on day 1, 30 mg/m² i.v. Adriamycin on day 1, 60 mg/m² i.v. cisplatin on day 1, and 3 mg/m² i.v. mitomycin C on day 1. The MCT regimen consisted of 4 mg/body i.v. mitomycin C and 30 mg/body i.v. cytosine arabinoside on days 1, 7, 14, 21 and 28 and 600 mg oral tegaful every day. The CAPM regimen was continued at 3- to 4-week intervals, although for the MCT regimen tegaful alone was continued every day until tumor progression.

Radiation therapy was carried out in the primary tumor, hilum and mediastinum only in patients at stage III. A total dose of 40–60 Gy was delivered at 2 Gy daily in 20–30 fractions on days 21–28 after two courses of chemotherapy in CAPM-treated patients but was delivered concurrently in MCT-treated patients. After the completion of radiotherapy, the CAPM regimen was resumed at the time at which hematologic recovery (WBC count, $\geq 4{,}000/mm^3$; platelet count, $\geq 10 \times 10^4/mm^3$) was attained. Cisplatin was given i.v. 2 h after prehydration with 1,000 ml 5% dextrose in 0.5 *N* saline, followed by another 1,000 ml normal saline. Then, 12 g mannitol was injected in successive i.v. boluses to induce diuresis.

The tumor response was assessed after the second course of the CAPM regimen and the first course of the MCT regimen. However, stage-III patients who had undergone combined chemo-radiotherapy were evaluated for response after the completion of radiation therapy. A complete response (CR) was defined as the complete disappearance of the primary tumor and all metastases. A partial response (PR) was defined as a reduction of >50% in the size of the primary disease as well as all metastases. Progressive disease (PD) was considered to represent an increase of >25% in one or more measurable lesions or the appearance of new lesions. All other conditions were classified as no change (NC).

Survival was evaluated from the beginning of chemotherapy, and the duration of the response was defined as the period from the beginning of the response due to chemotherapy until the day of the first observation of progressive disease. Both curves were calculated using the Kaplan-Meier method. Statistical comparisons of our analyses were made using the generalized Wilcoxon-Gehan test, the log-rank test and the chi-square test.

Results

Patient characteristics

Between July 1983 and June 1985, 136 patients were entered into the study. In all, 17 patients could not be evaluated: 14 received one cycle only or refused any further therapy, and 3 were lost to follow-up. Thus, 119 patients were evaluable for response and toxicity. Characteristics of the eligible patients are shown in Table 1. Both patient groups on the CAPM and MCT arms were balanced as far as sex, age, extent of disease and PS were concerned. There was no significant difference between the treatment groups.

Response rates

As shown in Table 2, the overall response rate was 34% for the CAPM arm and 13% for the MCT arm; the difference was statistically significant ($P < 0.001$). However, this sig-

Table 2. Objective tumor response, response duration and survival

	CAPM: Stage III	CAPM: Stage IV	CAPM: All	MCT: Stage III	MCT: Stage IV	MCT: All
Number of evaluable patients	15	43	58	15	46	61
Number of patients with:						
PR	6 (40%)	14 (33%)*	20 (34%)**	6 (40%)	2 (4%)	8 (13%)
NC	7 (47%)	22 (51%)	29 (50%)	8 (53%)	26 (57%)	34 (56%)
PD	2 (13%)	7 (16%)***	9 (16%)****	1 (7%)	18 (39%)	19 (31%)
Median response duration (months)	5.5	5.0****	5.0****	4.5	3.0	3.0
Median survival (months)	10.0	10.0**	9.5**	11.5	5.5	6.5

* $P < 0.001$; ** $P < 0.01$; *** $P < 0.02$; **** $P < 0.05$

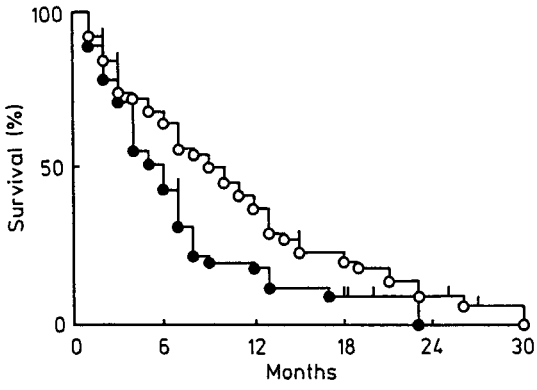

Fig. 2. Survival curves for the 136 eligible patients treated with the CAPM and MCT regimens. O, CAPM ($n = 69$); ●, MCT ($n = 67$). $P < 0.035$ according to the Wilcoxon-Gehan test; $P < 0.1$ according to the log-rank test

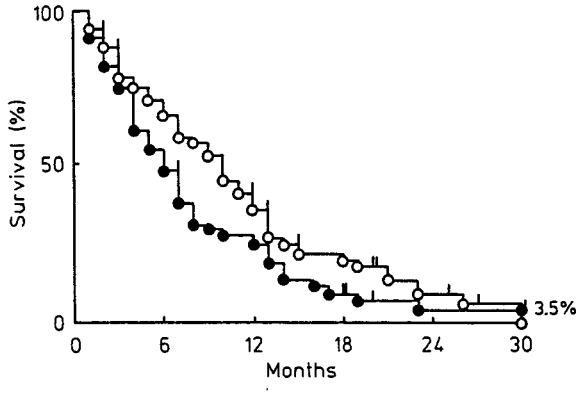

Fig. 4. Survival curves for the 100 eligible stage-IV patients treated with the CAPM and MCT regimens. O, CAPM ($n = 51$); ●, MCT ($n = 49$). $P < 0.025$ according to the Wilcoxon-Gehan test; $P < 0.05$ according to the log-rank test

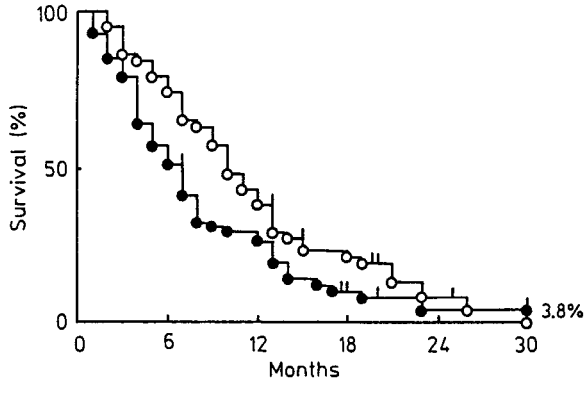

Fig. 3. Survival curves for the 119 evaluable patients treated with the CAPM and MCT regimens. O, CAPM ($n = 58$); ●, MCT ($n = 61$). $P < 0.007$ according to the Wilcoxon-Gehan test; $P < 0.05$ according to the log-rank test

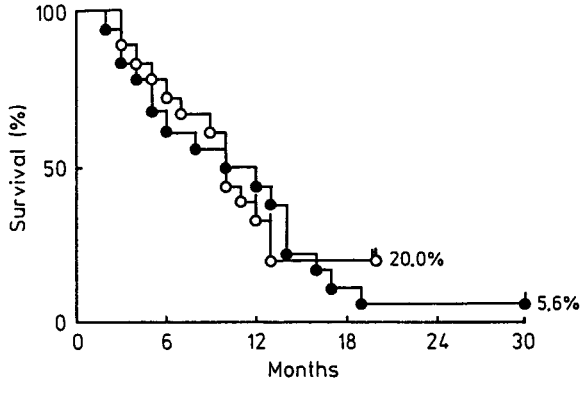

Fig. 5. Survival curves for the 36 eligible stage-III patients treated with the CAPM and MCT regimens. O, CAPM ($n = 18$); ●, MCT ($n = 18$). $P < 0.99$ according to the Wilcoxon-Gehan test; $P < 0.95$ according to the log-rank test

nificant difference was observed only in stage-IV patients treated with chemotherapy alone (CAPM, 33%; MCT, 4%), whereas in stage-III patients treated with combined chemoradiotherapy, there was no significant difference.

Response duration

The response duration for patients achieving a PR vs NC was compared between the two groups. As shown in Fig. 1, patients treated with the CAPM regimen had a median response duration of 5 months as opposed to 3 months for those treated with the MCT regimen ($P < 0.05$, Wilcoxon-Gehan test). However, the significant difference was observed only in stage-IV patients (CAPM, 5 months; MCT, 3 months; $P < 0.03$, Wilcoxon-Gehan test).

Survival

The median overall period of survival for all 136 patients was 9.5 months for the CAPM arm and 5.5 months for the MCT arm. The difference was significant ($P < 0.035$) according to the Wilcoxon-Gehan test but not according to the log-rank-test ($P < 0.1$) (Fig. 2). For the 119 evaluable patients, the median overall survival was 9.5 months for the CAPM arm and 6.5 months for the MCT arm; the difference was also significant ($P < 0.007$, Wilcoxon-Gehan test; $P < 0.05$, log-rank test) (Fig. 3). However, the improved survival of patients treated with the CAPM regimen was noted in stage-IV patients but not in stage-III patients as compared with those given the MCT regimen (Figs. 4, 5). Response to therapy was associated with improved survival. The median survival of responders to the CAPM regimen was 12 months and that of non-responders was 9 months; this difference was statistically significant ($P < 0.05$) according to the Wilcoxon-Gehan test but not according to the log-rank test ($P < 0.5$). Responders treated with the MCT regimen had a median survival of 13.5 months, whereas non-responders had a median survival of 5 months; this difference was also significant ($P < 0.008$, Wilcoxon-Gehan test; $P < 0.05$, log-rank test).

Toxicity

The hematologic and renal toxicity due to treatment is shown in Table 3. Leukopenia was more common in patients given the CAPM regimen than in those on the

Table 3. Toxicity of treatment

	CAPM	MCT
Lowest leukocytic count (/mm³):		
≥ 3,001	28/57 (49.1%)*	46/57 (80.7%)
2,001–3,000	11/57 (19.3%)	6/57 (10.5%)
1,001–2,000	12/57 (21.1%)	5/57 (8.8%)
≤ 1,000	6/57 (10.5%)**	0/57 (0%)
Lowest hemoglobin count (g/dl):		
≥ 12.1	10/57 (17.5%)	16/57 (28.1%)
11.1–12.0	6/57 (10.5%)	11/57 (19.3%)
10.1–11.0	15/57 (26.3%)	14/57 (24.6%)
≤ 10.0	26/57 (45.6%)	16/57 (28.1%)
Lowest platelet count (/mm³):		
≥ 15.1	35/55 (63.6%)	38/53 (71.7%)
10.1–15.0	14/55 (25.5%)	7/53 (13.2%)
5.1–10.0	3/55 (5.5%)	7/53 (13.2%)
≤ 5.0	3/55 (5.5%)	1/53 (1.9%)
Maximal serum creatinine (mg/dl):		
≥ 1.51	2/56 (3.6%)	2/54 (3.7%)
1.21–1.50	3/56 (5.4%)	3/54 (5.6%)
≤ 1.20	51/56 (91.1%)	49/54 (90.7%)
Nausea and vomiting	41/57 (71.9%)*	3/59 (5.1%)
Alopecia	47/57 (82.5%)*	5/59 (8.5%)

* $P < 0.001$; ** $P < 0.02$

MCT arm. Although anemia occurred more frequently in patients treated with the CAPM regimen, the difference was not significant. Thrombocytopenia was mild in both treatment groups. Nephrotoxicity, defined as a peak serum creatinine value of >1.5 mg/dl, occurred in two patients in each treatment arm. However, in these patients the serum creatinine value returned to normal ranges without specific treatment. Gastrointestinal toxicity with nausea and vomiting or alopecia occurred in 71.9% and 82.5%, respectively, of all patients treated with the CAPM regimen and was significantly higher than that observed in those treated with the MCT regimen.

Discussion

Although it has been demonstrated that patients who respond to chemotherapy live longer than non-responders, the question as to whether chemotherapy improves overall survival remains unproven.

The data from the present study shows that CAPM therapy significantly increased the response rate and improved survival in comparison with the MCT regimen. In this study, the MCT regimen [8] was used as the control arm because we commonly gave this regimen in our Japanese practice before we adopted the use of intensive multidrug combinations. The median survival of 6 months for the MCT arm was comparable with that demonstrated in previous studies. Therefore, there is no indication that the MCT arm had a negative effect on the survival of patients in this study. However, the benefits of intensive combination chemotherapy are controversial, with three studies [3, 4, 9] having reported improved survival and two others [6, 14] reporting no improvement in survival.

A recent study by the National Cancer Institute of Canada [9] compared patients treated with vindesine plus cisplatin or with cyclophosphamide, Adriamycin and cisplatin (CAP) with the control group given only supportive care. This study demonstrated that the survival of patients in both chemotherapy arms were superior to those in the supportive-care arm. Comier et al. [3] and Elliott et al. [5] also demonstrated the survival benefits for patients treated with polychemotherapy vs those treated with a single agent or placebo. In contrast, the data reported by Woods et al. [14] and Ganz et al. [6] differed from our results. These authors compared patients treated with cisplatin plus vindesine or with cisplatin plus vinblastine with those receiving supportive care, respectively, demonstrating no significant difference in survival. Thus, under the present circumstances, one should consider that intensive combination chemotherapy does not always benefit patients with advanced NSCLC.

In the present study, the survival advantages for patients treated with the CAPM regimen were observed in stage-IV patients but not in stage-III patients. The difference is probably caused by the fact that all stage-III patients received radiation therapy in the primary site and the mediastinum. Since radiation therapy is the most active treatment modality for locally advanced disease, it is possible that the effect of chemotherapy on survival could be obscured by the addition of radiation therapy. On the other hand, the reason for the survival benefits for stage-IV patients treated with the CAPM regimen is not clear. However, the survival of patients has been reported to be influenced by prognostic factors such as sex, performance status, extent of disease and response rate [1, 13]. Prognostic factors in our study were similar in both treatment groups, except that there were more responders in the CAPM arm. In fact, responders showed significantly longer survival than non-responders, as shown in *Results*. Thus, we believe that a high response rate is responsible for improved survival in patients treated with the CAPM regimen. In addition, the prolonged response duration observed in the CAPM arm may also be associated with improved survival.

Myelosuppression and gastrointestinal toxicities were most commonly experienced in patients on the CAPM arm, and the extent of these toxicities was more severe than that in patients on the MCT arm. However, there were no treatment-related deaths. All levels of toxicity were acceptable.

In conclusion, the present study confirms that intensive chemotherapy containing cisplatin significantly increased the response rate and improved survival to a great extent. However, treatment-related toxicities were also increased. Considering the toxicity and the minor survival benefits attained, it is questionable as to whether intensive chemotherapy is worthwhile in the treatment of NSCLC. To address this question, further studies using the most effective chemotherapy regimen for NSCLC are necessary.

Appendix

Institutions	Investigators
National Kyushu Cancer Center	M. Ohta, N. Hara, A. Motohiro
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Chikugo City Hospital	F. Tanaka
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Nagasaki City Shimin Hospital	S. Nakano, A. Ikebe, K. Komori
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Shimabara Prefectural Hospital	J. Araki
Kumamoto Shimin Hospital	K. Shima, Y. Takenaka, S. Higuchi, K. Fukuda
Kumamoto Rohsai Hospital	Y. Fukuda, K. Tokunaga
Minamata City Hospital	K. Kitano
Miyazaki Prefectural Hospital	K. Tamura, Y. Araki
Ryukyu University	M. Hokama
National Okinawa Hospital	M. Kuba, K. Nakasone
Fukuoka University	T. Shigematsu

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