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A prognostic-factor risk index in advanced non-small-cell lung cancer treated with cisplatin-containing combination chemotherapy*

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Summary. Prognostic factors for response and survival were retrospectively evaluated in 192 previously untreated patients with advanced non-small-cell lung cancer (NSCLC) who had received either vindesine plus cisplatin or mitomycin plus vindesine plus cisplatin as initial treatment. Univariate analysis demonstrated that squamous-cell histology, early stage, and a small number of metastatic sites were favorable prognostic factors for response to chemotherapy. Multivariate analysis using Cox's proportional hazard model indicated that the number of metastatic sites was the only significant pretreatment factor for response ($P = 0.0005$). Multivariate regression analysis revealed that the number of metastatic sites ($P = 0.0002$), sex ($P = 0.0009$), serum albumen levels ($P = 0.0018$), performance status ($P = 0.0026$) and lactic dehydrogenase values ($P = 0.0026$) contributed independently to survival. On the basis of these five prognostic factors, a prognostic index for survival was used to define three prognostic groupings (good, intermediate, and poor) for survival (median survival, 16.5 vs 9.4 vs 4.6 months; $P = 0.0001$). This particular regression model should aid in the design and analysis of new treatment strategies and may be useful for indirect comparisons of different studies carried out in similar patient populations.

Introduction

Since the introduction of cisplatin-based chemotherapy, various studies have shown that a variety of combination regimens produce rates of response in the range of 25%–50% in patients with non-small-cell lung cancer (NSCLC) [1, 11]. Recently, a randomized study has suggested that chemotherapy produces a small but significant improvement in survival [16]. However, the outcome of patients with advanced NSCLC remains poor in general, and the magnitude of differences in outcome for categories of the strongest prognostic factors are larger than those for the type of therapy used [5, 12, 17, 22]. Therefore, knowledge of prognostic factors is essential to the prognosis of advanced NSCLC and to the planning and analysis of clinical trials in patients with this disease.

The prognosis for patients with inoperable lung cancer may vary with respect to the era during which treatment has been received [4, 18] and to the chemotherapy regimen given [12]. Therefore, the current retrospective analysis represents a single-institution review based on consistent initial staging, primary treatment using cisplatin- and vindesine-based combination chemotherapy, and a consistent approach to supportive care. On the basis of the analyses for major prognostic factors, a new type of prognostic index was proposed to define three prognostic groupings for survival.

Patients and methods

Patients. The present series included 192 previously untreated patients with histologically or cytologically proven advanced NSCLC. Of these, 186 individuals had participated in 1 of 3 consecutive prospective, randomized trials of combination chemotherapy {vindesine plus mitomycin vs vindesine plus cisplatin (80 mg/m^2) [19], modest-dose cisplatin (80 mg/m^2) vs high-dose cisplatin (120 mg/m^2) with a fixed dose of vindesine [20], and vindesine plus cisplatin (80 mg/m^2) vs mitomycin plus vindesine and cisplatin (80 mg/m^2) [21]}, and 6 others received mitomycin plus vindesine plus cisplatin in a phase II study carried out from July 1982 until March 1989 at the National Cancer Center Hospital, Tokyo. Ten patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 3 were excluded because of their uniformly poor prognosis.

All 192 patients were treated with either a combination of vindesine and cisplatin or a combination of mitomycin, vindesine, and cisplatin. In the former regimen, cisplatin was given i. v. at a dose of 80 or 120 mg/m^2

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every 3–4 weeks for three cycles and every 6 weeks thereafter, and vindesine (3 mg/m^2) was given by rapid i. v. injection once a week for the first 5 weeks and every 2 weeks thereafter. In the latter regimen, patients received 8 mg/m^2 mitomycin on day 1, 3 mg/m^2 vindesine on days 1 and 8, and 80 mg/m^2 cisplatin on day 1, with treatments being given three times every 4 weeks and then every 6 weeks. The overall response rate was 29%, the median survival was 10.0 months, with no differences being observed between the treatment arms or the protocols.

Response and survival assessment. Before the initiation of therapy, all patients underwent a complete physical examination, including a full clinical assessment, a chest X-ray, a complete blood count and biochemistry, a bone marrow examination, a radionuclide bone scan and plain bone roentogenography, computerized tomography of the brain and thorax, and computerized tomography and/or an ultrasound examination of the abdomen. Needle puncture or biopsy was carried out if pleural fluid, pericardial fluid, or superficial foci were observed. On the basis of these staging procedures, patients were characterized as having either limited or extensive disease [24]. The response to chemotherapy was assessed after three cycles of treatment, response being defined as a reduction of >50% in the sum of the products of the two greatest perpendicular diameters of all indicator lesions for at least 4 weeks without the appearance of new lesions or progression of any preexisting lesion. Survival was recorded from the 1st day of treatment. A follow-up period of >1 year was required for analysis of the results.

Factors analyzed. The pretreatment factors analyzed included age; sex; ECOG performance status (PS) [27]; weight loss over the previous 6 months, histology; stage of disease [13]; extent of disease [24]; number of metastatic sites; distant metastatic sites at presentation (central nervous system, liver, and bone); hemoglobin value; total lymphocyte count; levels of serum albumen, serum cholesterol, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and serum carcinoembryonic antigen (CEA); and treatment received. The selection of these pretreatment variables was made by considering three factors: clinical relevance, risk ratio, and statistical significance. Calculations of the number of metastatic (organ) sites did not distinguish between single and multiple metastasis in a given organ in patients with stage IV disease; for example, a multiple bone metastasis, multiple brain metastasis, or multiple skin metastasis was calculated as one site.

Statistical methods. The chi-square test was used to evaluate differences in the response rate. The logistic multiple regression model was used to define the dependent variable for response [26]. Survival curves were calculated according to the method of Kaplan and Meier [10]. Significance tests were based on log-rank analysis [15]. For determination of the most significant variables related to survival, Cox's proportional hazards model was used [3]. Forward and backward stepwise regression procedures based on the partial likelihood ratio were applied to determine the factors that were important and independent predictors of survival. A P value of 0.05 or less was set as the limit for inclusion in the model.

All patients were assigned a prognostic index value based on the final model. In particular, the value for each factor in the final model was multiplied by its corresponding regression coefficient, and the results obtained for all of the factors were added together in the final model to form the prognostic index for each patient. Grouping was then carried out on the basis of this prognostic index, and rates as well as curves for 1- and 2-year survival were calculated for patients in the separate groups. All P values presented in this report are of the two-sided type.

Results

The analysis of the pretreatment characteristics and of their association with tumor response revealed that histology (non-squamous adenocarcinoma, 135 patients; large-cell carcinoma, 17 subjects; adeno-squamous carcinoma, 5 cases; $P = 0.017$), stage of disease ($P = 0.005$), extent of disease ($P = 0.029$), and number of metastatic sites ($P = 0.002$) were significantly related to response (Table 1).

For the identification of factors that showed an important and independent association with tumor response, a logistic regression model was applied using a stepwise procedure. The first variable entered was the number of metastatic sites ($P = 0.0005$) with the variate in the model, and the next variable entered was sex ($P = 0.0504$). However, the number of metastatic sites was the most important and independent variable associated with tumor response ($\beta = 0.7861$, SE = 0.2253; $P = 0.0005$).

Among the 192 patients studied, 18 (9%) are alive at the present time. Thus, the follow-up period used was sufficiently long to yield high statistical power for the detection of important relationships between prognostic factors and survival, as the power of the present statistical test is based on the total number of deaths, not on the total number of patients.

The results of the univariate analyses are summarized in Table 1. A statistically significant prognostic influence was observed for sex ($P = 0.020$), PS ($P = 0.0001$), prior weight loss ($P = 0.002$), stage of disease ($P = 0.021$), disease extent ($P = 0.009$), number of metastatic sites ($P = 0.0001$), central nervous system (CNS) metastasis ($P = 0.026$), liver metastasis ($P = 0.008$), bone metastasis ($P = 0.021$), serum albumen levels ($P = 0.0001$), and ALP ($P = 0.031$) and LDH ($P = 0.0002$) values.

Multivariate regression analyses were conducted to identify the factors that independently had the most important prognostic impact on survival in 169 patients for whom none of the values for the variables was missing. Among the 19 variables tested, the number of metastatic sites, sex, serum albumen levels, PS, and LDH values remained significantly related to survival at the end of the multiple regression analysis (Table 2). The significant influence on survival found in univariate analyses for prior weight loss, stage, disease extent, CNS metastasis, liver metastasis, bone metastasis, and ALP values were omitted from the final multivariate model because they added no further predictive information following adjustment for the other covariates included in the model. The same held true for forward and backward analyses.

Female gender was a favorable prognostic factor ($P = 0.0009$); this variable demonstrated a significantly higher proportion of non-squamous carcinoma ($P = 0.004$), a higher advanced stage of disease ($P = 0.001$), a larger number of metastatic sites ($P = 0.006$), a lower hemoglobin level ($P = 0.002$), and a lower Brinkman index [18] of smoking ($P = 0.002$) than did male gender. PS, serum albumen levels, and ALP and LDH values did not differ significantly between women and men. When the likelihood-ratio test of adding sex to the four-variable model (number of metastatic sites, PS, albumen levels, and LDH value) was performed, the likelihood-ratio chi-square value for sex was 11.7 ($P = 0.0006$).

For clinical use in individual patients, the estimation of the prognostic index was based on regression coefficients derived from the five variables in Table 2. The equation used to calculate the index was: 0.4253 x (if the number of

Table 1. Univariate analysis of pretreatment factors in patients with advanced NSCLC for their value in predicting response and survival

Variable	Patients (*n*)	Responders (*n*)	Response rate (%)[a]	Median survival (months)	*P* value for survival[b]
Sex:					0.020
F	55	19	34.5 (22.0–47.1)	14.6	
M	137	37	27.0 (19.6–34.4)	9.1	
Age:					0.09
< 60 years	86	26	30.2 (20.5–39.9)	9.4	
≥60 years	106	30	28.3 (19.7–34.4)	10.2	
Performance status:					0.0001
0	26	8	30.8 (13.0–48.5)	17.5	
1	138	43	31.2 (23.4–38.9)	10.2	
2	28	5	19.9 (3.7–32.0)	5.9	
Prior weight loss (≥10%):					0.002
No	139	43	30.9 (23.3–38.6)	10.8	
Yes	34	8	23.5 (9.3–37.8)	6.3	
Histology:					0.94
Squamous	35	16	45.7 (29.2–62.2)	9.6	
Non-squamous	157	40	25.4 (18.7–32.3)	10.2	
Stage:					0.021
IIIA	22	11	50.0 (29.1–70.9)	14.0	
IIIB	42	17	40.5 (25.6–55.3)	10.2	
IV	128	28	21.9 (14.7–29.0)	8.3	
Disease extent:					0.009
Limited	83	31	37.3 (26.9–47.8)	11.3	
Extensive	109	25	22.9 (15.0–30.8)	8.3	
Metastatic sites (*n*):					0.0001
0	64	28	43.8 (31.6–55.9)	10.7	
1	76	21	27.6 (17.6–37.7)	11.8	
≥2	52	7	13.5 (4.2–22.7)	6.5	
CNS metastasis:					0.026
Absent	178	51	28.7 (22.0–35.3)	10.0	
Present	14	5	35.7 (10.6–60.8)	7.9	
Liver metastasis:					0.008
Absent	179	55	30.7 (24.0–37.5)	10.2	
Present	13	1	7.7 (1.4–33.3)	5.4	
Bone metastasis:					0.021
Absent	133	43	32.3 (24.4–40.3)	10.5	
Present	59	13	22.0 (11.5–32.6)	8.1	
Hemoglobin:					0.074
> 11.0 mg/dl	161	46	28.6 (21.6–35.5)	10.2	
≤11.0 mg/dl	31	10	32.3 (15.8–48.7)	6.8	
Total lymphocyte count:					0.37
≥1,500/mm^3	134	38	28.4 (20.7–36.0)	10.2	
< 1,500/mm^3	58	18	31.0 (19.1–42.9)	9.5	
Serum albumen:					0.0001
≥3.7 g/dl	141	46	32.6 (24.3–41.8)	11.3	
< 3.7 g/dl	51	10	20.0 (10.6–29.5)	5.9	
Serum cholesterol:					0.19
≥150 mg/dl	142	40	28.2 (20.8–35.6)	10.4	
< 150 mg/dl	30	9	30.0 (13.6–46.4)	7.8	
Alkaline phosphatase:					0.031
≤230 IU/l	147	45	30.8 (23.3–38.3)	10.2	
> 230 IU/l	45	11	24.4 (11.9–37.0)	8.3	
Lactate dehydrogenase:					0.0002
≤350 IU/l	123	39	31.7 (23.5–40.0)	11.3	
> 350 IU/l	69	17	24.6 (14.5–34.8)	8.1	
Serum carcinoembryonic antigen:					0.71
< 5 ng/ml	53	17	32.1 (22.1–45.7)	9.6	
≥5–<20 ng/ml	54	13	24.1 (8.3–31.7)	10.7	
≥20 ng/ml	85	26	30.6 (20.8–40.4)	9.7	
Treatment:					0.39
MMC+VDS+CDDP	67	21	31.3 (20.2–42.4)	10.2	
VDS+CDDP	125	35	28.0 (20.1–35.9)	9.9	

[a] 95% CI shown in parentheses

[b] According to a two-sided log-rank test

MMC, Mitomycin C; VDS, vindesine; CDDP, cisplatin

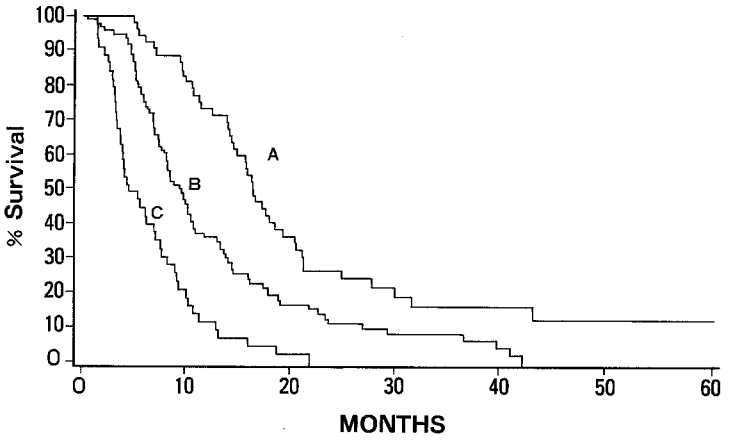

Fig. 1. Survival of patients grouped into the categories in the Cox model according to the following prognostic indices: <1.3 (*A*, 52 subjects), ≥1.3–<2.2 (*B*, 96 patients), and ≥2.2 (*C*, 44 subjects)

Table 2. Prognostic factors in NSCLC: results of Cox regression analysis

Variable	Coefficient (β)	SE	Risk ratio[a]	95% CI	*P* value
Number of metastatic sites	0.4253	0.1130	1.53	1.23–1.91	0.0002
Sex	0.6116	0.1840	1.84	1.29–2.64	0.0009
Serum albumen	0.4936	0.1583	1.64	1.20–2.23	0.0018
Performance status	0.4664	0.1549	1.59	1.18–2.16	0.0026
Lactate dehydrogenase	0.5242	0.1743	1.69	1.20–2.38	0.0026

[a] Risk ratio per unit of change

Table 3. Number of 1- and 2-year survivors, median survival and response rate according to prognostic indices for the Cox model

Prognostic index	Number of patients: total/dead	Survival (%)		Median survival (months)	Response rate (%)[a]
		1-year	2-year		
<1.3	52/ 43	73.1	26.1	16.5	42.3
1.3–<2.2	96/ 87	36.0	11.0	9.4	30.2
≥2.2	44/ 44	11.6	0	4.6	11.6
Totals	192/174	40.4	12.5	10.0	29.2

[a] Complete responses + partial responses

metastatic sites is 0, code as 0; if 1, code as 1; and if ≥2, code as 2) + 0.6116 x (if the gender is female, code as 0; if male, code as 1) + 0.4936 x (if serum albumen levels are ≥3.7 g/dl, code as 0; if <3.7 g/dl, code as 1) + 0.4664 x (if the PS is 0, code as 0; if 1, code as 1; and if 2, code as 2) + 0.5242 x (if LDH values are ≤350 IU/l, code as 0; if >350 IU/l, code as 1). For example, in a man presenting with one metastatic site, a serum albumen level of 3.5 g/dl, a PS of 2, and an LDH value of 370 IU/l, the prognostic index would be 2.9875 (0.4253 × 1 + 0.6116 × 1 + 0.4936 × 1 + 0.4664 × 2 + 0.5242 × 1). The prognostic index ranged from 0 to 3.5123 in 192 patients.

To divide the patients into three prognostic groups (good, intermediate, and poor), we looked at survival curves at various breakpoints of the prognostic index with regard to the sample size in each group. As a result, the 192 patients were grouped according to prognostic indices of <1.3 (group A, 52 subjects), ≥1.3–<2.2 (group B, 96 patients), and ≥2.2 (group C, 44 cases), respectively. Survival curves generated for patients in these three categories are shown in Fig. 1. The level of statistical significance between the survival curves was $P = 0.0001$. The 1- and 2-year survival, median survival, and response according to prognostic indices are summarized in Table 3. There was a strong correlation between survival and the three prognostic categories ($P = 0.0001$). With respect to response, a strong relationship was found between the response rate and the three prognostic indices (chi-square test, $P = 0.005$).

Discussion

The prognosis of NSCLC remains poor despite the recent improvements in response rates achieved using combination chemotherapy. The current study was carried out to evaluate retrospectively the prognostic factors for response and survival in 192 previously untreated patients with advanced inoperable NSCLC who had received relatively uniform combination chemotherapy in the recent era. We confirmed the findings of other investigators that a good PS [5, 12, 14, 18, 23, 25], female gender [5, 12, 14, 18], a normal serum LDH value [14, 23], and a lower number of metastatic sites [14] are significant favorable prognostic factors for survival, whereas other variables such as stage or extent of disease [12, 23, 25], prior weight loss [5, 25], liver metastasis [5, 23], or initial lymphocyte count [25] fail to show additional prognostic value in advanced NSCLC.

Our findings are comparable with those of O'Connell et al. [14]. In the latter study and our current series, the initial PS, sex, the number of extrathoracic metastatic organ sites, and LDH values were found to be significantly associated with outcome in patients with inoperable NSCLC who received cisplatin- and vinca alkaloid-based combination chemotherapy, although bone metastasis did not have a significant influence in our series and serum albumen was not used as a variable in the previous study.

The impact of stage or disease extent on the prognosis for NSCLC has been reported in several studies [12, 23, 25]; however, the current investigation failed to con-

firm stage or extent of disease as a significant independent prognostic factor, and the Cox model remained practically unchanged when either of these variables was excluded. As significant independent prognostic factors, subsets within each of these variables perform better: N2 disease identified by mediastinoscopy vs bulky N2 disease [6] and minimal vs bulky disease in limited disease, extrathoracic vs intrathoracic involvement in extensive disease, and single-organ vs multiple-organ involvement. In the current study, the difference in survival between patients with no metastatic organ site and those with one such site was not significant (Table 1), and this finding is consistent with the data previously reported by Ihde et al. [8] for small-cell lung cancer. These observations could partly explain the lack of a major impact by stage or extent of disease on survival.

Sex contributed significantly to survival in three large studies on inoperable NSCLC [5, 12, 14], although gender was not significant in one study on inoperable adenocarcinoma of the lung [22]. The current investigation (adenocarcinoma, 70% of the study population) confirmed that women survived significantly longer than men, in agreement with our previous report [18]. In the present study, the incidence of squamous-cell carcinoma, early stage of disease, and fewer metastatic sites was observed to be significantly higher in men than in women. PS, levels of serum albumen, LDH values, and response to chemotherapy did not differ between women and men (data not shown).

Johnston-Early et al. [9] have reported that smoking abstinence prolongs the survival of small-cell lung cancer patients. In the current study, female gender had a significantly lower Brinkman index [2], but it remained unclear whether smoking had any impact on survival. Furthermore, the estimated β coefficient for the number of metastatic sites depends on whether sex or not is included in the model, and vice versa. Although sex and the number of metastatic sites were statistically significant ($P = 0.013$ and $P = 0.011$, respectively), with each showing approximately the same estimated β coefficient (0.4208 and 0.2745, respectively) when the other variable had been excluded from the model and with the likelihood-ratio chi-square value for sex being 11.7 ($P = 0.0006$), they were more highly significant when both variables had been included in the model than when one of them had been removed. These findings suggest that these two variables appear to be associated with one another and that sex may not be an independent prognostic factor.

The prognostic index for survival in the present patient population was composed of the number of metastatic sites, sex, serum albumen levels, PS, and LDH values (Table 2). Based on regression coefficients of these five prognostic factors, this prognostic index could be used to define three prognostic groups (good, <1.3; intermediate, $\geq 1.3 - <2.2$; poor, ≥ 2.2) for survival (median survival, 16.5 vs 9.5 vs 4.6 months, respectively; $P = 0.0001$; Table 3). None of the patients whose prognostic index was ≥ 2.8 survived for 10 months after the start of treatment. Our findings support the results of a study by Sørensen et al. [23] on prognostic index in advanced NSCLC, despite differences in index design. In the latter study, the prognostic index was based on a combination of PS, surgery, stage, white blood count, levels of aspartate aminotransaminase, LDH values, and liver metastasis. In contrast to the current study, Sørensen et al. included a surgical factor in a multivariate analysis, and the patients who received nonradical resection survived significantly longer than those who did not undergo surgery. Moreover, the patients who were candidates for surgery at presentation appeared to be a selected population because they presented with minimal disease or local spread of disease as described by the authors. Therefore, the regression model used in the current study appears to be of more practical importance for the design of future treatment strategies and may assist the clinician in making more accurate predictions and in answering questions posed by the patients or their families concerning the probable course of their disease in advanced inoperable NSCLC, although this new prognostic index is always more precise for groups of patients than for individuals.

This study analyzed a large number of variables for their potential prognostic value. The occurrence of false-positive errors when the ratio of the number of patients to the number of potential predictors is small (e.g., <10) has been addressed elsewhere [7]. The ratio obtained in the current study is close to that border [19 potential predictors, 192 patients (18 alive)].

The current study demonstrated that the number of metastatic sites was the most important prognostic factor for both response and survival in advanced NSCLC as previously described by other investigators [8, 14]; therefore, in future clinical trials the number of metastatic sites should be considered as a factor in stratification. As determined by multivariate analysis, sex, levels of serum albumen, PS, and LDH values were also significant prognostic factors in advanced NSCLC, and the prognostic index based on these five variables may help in the design of future treatment strategies in patients with inoperable NSCLC. The present cisplatin- and vinca alkaloid-based chemotherapy regimen is widely used in the treatment of patients with advanced NSCLC. The information obtained in the current analyses may be useful for comparisons of different studies carried out in similar patient populations.

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