Jpn. J. Cancer Res. **90**, 249–253, February 1999

Prognostic Factors for Short-term Survival in Patients with Stage IV Non-small Cell Lung Cancer

Masahiko Ando,[1,2] Yuichi Ando,[2] Seiji Sugiura,[2] Hironobu Minami,[3] Hideo Saka,[2] Shuzo Sakai,[1] Kaoru Shimokata[4] and Yoshinori Hasegawa[2,5]

[1]Department of Internal Medicine, Japanese Red Cross Nagoya First Hospital, 3-35 Michishita-cho, Nakamura-ku, Nagoya 453-8511, [2]First Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, [3]National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-0882 and [4]Clinical Preventive Services, Nagoya University School of Medicine, 1-1-20 Taiko-Minami, Higashi-ku, Nagoya 461-0047

Prognostic factors which can forecast short-term survival in patients with stage IV non-small cell lung cancer have not been well evaluated. Characteristics of such factors may be different from those for overall survival, and would be an important eligibility criterion for clinical trials of chemotherapy. We retrospectively analyzed the data of 158 patients with stage IV non-small cell lung cancer whose performance status was 0, 1 or 2. Univariate and multivariate logistic regression models revealed demographic variables which significantly correlated with the survival at 8 or 12 weeks. The univariate model showed the following significant variables: T factor, N factor, number of organs with metastases, grade of performance status, weight loss within 6 months, evidence of metastasis either at bone or lymph node, and lactate dehydrogenase level. The subsequent multivariate model demonstrated that both grade of performance status under 2 and number of metastasized organs less than 3 are important factors for 8- or 12-week survival. The survival rate in patients meeting the two criteria (grade of performance status under 2 and number of metastasized organs less than 3) and in those meeting only one of them was 93% versus 80% at 8 weeks (P=0.030) and 88% versus 62% at 12 weeks (P<0.001), respectively. Grade of performance status and number of organs with metastases appear to be important prognostic factors for short-term survival in patients with stage IV non-small cell lung cancer.

Key words: Minimum life expectancy — Non-small cell lung cancer — Performance status — Metastasis

The median survival of patients with stage IV non-small cell lung cancer is around 6 months,[1)] and several factors have been identified to forecast each patient's prognosis in more detail.[2–7)] A more individualized prognosis helps the physician to determine what therapy and/or supportive care should be suitable for each patient and how to explain the prognosis to the patient.

At present, the benefits of chemotherapy for patients with non-small cell lung cancer are not very satisfactory, and patients with incurable stage IV disease are candidates for clinical trials of chemotherapy. These patients might obtain some anti-tumor effects from investigational treatment. However, clinical investigators should exclude patients with very poor prognosis, for example, with less than 8-week survival, from such a study. Systemic chemotherapy would not have any survival benefits for patients with a very poor prognosis. Furthermore, it is difficult to evaluate the anti-tumor effect and adverse effects of a drug under investigation during a very short period of less than 8 weeks. Eligibility criteria for clinical trials usually include a minimum life expectancy of 8 or 12 weeks in order to maximize the chance for patients to benefit from treatment and to allow adequate evaluation of the agent under investigation.[8)] However, the minimum life expectancy is, in general, estimated subjectively based on the physician's experience or feeling, because no objective information on short-term survival is available. Estimation of the patient's prognosis by a physician is often overoptimistic and unreliable,[9)] and might lead to recruitment of unsuitable patients in a study. It is also undesirable for the patients, and may lead to difficulty in the interpretation of the results of the study. Therefore, we believe that more objective information on factors suitable for forecasting short-term survival is necessary. The characteristics of such factors may be different from those for overall survival, and would be important as eligibility criteria of clinical trials of chemotherapy. The present study was conducted to find prognostic factors, which predict the short-term prognosis of patients with stage IV non-small cell lung cancer.

PATIENTS AND METHODS

Patients The clinical records of 535 consecutive patients with histologically or cytologically confirmed non-small

[5] To whom correspondence should be addressed.
E-mail: yhasega@tsuru.med.nagoya-u.ac.jp

cell lung cancer, who were admitted to the Japanese Red Cross Nagoya First Hospital between January 1989 and December 1996, were retrospectively reviewed. We excluded patients with recurrent lung cancer in this study. Among these patients, 222 had stage IV disease at the initial staging procedure described below. Fifty-six patients with performance status of 3 and 4 were excluded because patients with such poor performance status are not candidates for clinical trials. Six patients who underwent incomplete staging and two patients lost to follow-up before 12 weeks were also excluded. The remaining 158 patients (median age, 65.5 years; range, 30–99 years) were the subjects of the present analysis.

Staging procedure Patients were staged according to the TNM system.[1)] All 158 patients underwent the following procedures on presentation: medical history, physical examination, histologic or cytologic confirmation of non-small cell lung cancer, complete blood cell count, platelet count, serum chemistry, chest radiograph and computed tomography (CT), abdominal CT and/or ultrasonography, brain CT, and radionuclide bone scan. Bone radiographs were used to confirm metastasized lesions suspected on the basis of the bone scan. Bronchoscopic examination was not performed in all cases. Mediastinal lymph nodes were evaluated by chest CT without confirmation by mediastinoscopy.

Demographic and clinical factors The following factors were evaluated: age, sex, histology, extent of primary lesion (T factor), involvement of regional lymph nodes (N factor), evidence of metastasis at brain, liver, bone, lung, lymph node, or adrenal gland (M factor), number of organs with metastasized lesions, grade of performance status, weight loss over 5% in the 6 months before diagnosis, hemoglobin level, serum albumin level, and serum lactate dehydrogenase (LDH) level. Since the imbalance in the patients' characteristics between those treated with and without chemotherapy was too large, we could not evaluate the effect of chemotherapy as a single factor. When the number of organs with metastasized lesions was evaluated, an organ with multiple metastases was counted as one.

Statistical methods Survival was calculated from the date of pathological diagnosis. All factors which had more than two categories, or were continuous, were dichotomized at the points that reflected the greatest difference in survival. The logistic regression model identified significant and independent prognostic factors for survival at 8 or 12 weeks using JMP ver. 3.0.2 software (SAS Institute Inc., Cary, NC). Initially, the difference between subgroups with or without each risk factor was evaluated with a univariate logistic regression model. The factors were considered significant when the P value was under 0.05, and were evaluated in the subsequent analysis. The unconditional multivariate logistic regression model using forward and backward stepwise procedures was used to confirm the important factors affecting the survival at 8 or 12 weeks.

RESULTS

Among the 158 patients analyzed, 56 were entered into clinical chemotherapy trials, 31 were treated with chemotherapy in non-protocol settings, and the remaining 71 received best supportive care alone. The survival rates of all patients analyzed were 87% (95% confidence interval: 81–92%) and 78% (71–84%) at 8 and 12 weeks, respectively. The univariate model showed the following variables significant for survival at 8 or 12 weeks; T factor, N factor, number of organs with metastases, grade of performance status, weight loss within 6 months, evidence of metastasis either at bone or lymph node, and LDH level (Table I). The subsequent multivariate model demonstrated that grade of performance status under 2 plus a number of metastasized organs of less than 3 is an important condition for both 8- and 12-week survivals (Table II). The actual survival rates showed that 88% of the patients with performance status under 2 and a number of metastasized organs of less than 3 were alive at 12 weeks and that they were the major population (66%) among the patients analyzed in the present study (Table III, Fig. 1). The survival rates of patients meeting both conditions and those meeting only one of them were 92% versus 80% at 8 weeks (P=0.030) and 88% versus 62% at 12 weeks (P<0.001), respectively. The three patients with performance status of 2 and a number of metastasized organs of more than 2 died within 8 weeks. The 87 patients treated with chemotherapy were analyzed separately from those with best supportive care alone. The survival rates of the 65 patients meeting the two conditions (performance status under 2 and metastasized organs less than 3) were both 97% at 8 and 12 weeks, while those of the 22 patients not meeting both criteria were 77% at 8 weeks (P=0.006, χ^2 test) and 68% at 12 weeks (P<0.001). On the other hand, when we analyzed the 71 patients with best supportive care alone, the differences in survival remained significant (P=0.029 at 8 weeks and P=0.042 at 12 weeks).

DISCUSSION

The present study demonstrated that grade of performance status and number of organs with metastases might be important prognostic factors for short-term survival in patients with stage IV non-small cell lung cancer; more than 85% of patients with performance status under 2 and with a number of metastasized organs of less than 3 were alive after 12 weeks. The result remained valid when we excluded the patients who did not receive chemotherapy.

Table I. Relationships between Demographic Variables and Survival at 8 or 12 Weeks in Patients with Stage IV Non-small Cell Lung Cancer

Demographic variables	Number of patients	Survival at 8 weeks (%)	*P* by logistic analysis	Survival at 12 weeks (%)	*P* by logistic analysis
Age					
<75	130	114 (87.7)	0.435	104 (80.0)	0.165
≥75	28	23 (82.1)		19 (67.9)	
Sex					
Male	103	86 (83.5)	0.113	77 (74.8)	0.204
Female	55	51 (92.7)		46 (83.6)	
Histology					
Squamous	32	29 (90.6)	0.468	27 (84.4)	0.323
Other	126	108 (85.7)		96 (76.2)	
T factor					
0–3	98	89 (90.8)	0.057	82 (83.7)	0.026
4	60	48 (80.0)		41 (68.3)	
N factor					
0–2	96	88 (91.7)	0.027	80 (83.3)	0.041
3	62	49 (79.0)		43 (69.4)	
Number of metastasized organs					
1–2	137	123 (89.8)	0.006	112 (81.8)	0.004
>2	21	14 (66.7)		11 (52.4)	
Brain metastasis					
Yes	33	29 (87.9)	0.824	23 (69.7)	0.208
No	125	108 (86.4)		100 (80.0)	
Liver metastasis					
Yes	18	15 (83.3)	0.655	13 (72.2)	0.543
No	140	122 (87.1)		110 (78.6)	
Bone metastasis					
Yes	67	53 (79.1)	0.020	45 (67.2)	0.007
No	91	84 (92.3)		78 (85.7)	
Lung metastasis					
Yes	76	66 (86.8)	0.962	60 (78.9)	0.749
No	82	71 (86.6)		63 (76.8)	
Adrenal metastasis					
Yes	14	11 (78.6)	0.355	10 (71.4)	0.547
No	144	126 (87.5)		113 (78.5)	
Lymph node metastasis					
Yes	26	19 (73.1)	0.031	16 (61.5)	0.033
No	132	118 (89.4)		107 (81.1)	
Performance status					
0–1	123	111 (90.2)	0.018	103 (83.7)	0.001
2	35	26 (74.3)		20 (57.1)	
Weight loss in 6 months					
≥5%	68	53 (77.9)	0.007	47 (69.1)	0.024
<5%	90	84 (93.3)		76 (84.4)	
Hemoglobin level					
≥11 g/dl	126	111 (88.1)	0.313	102 (81.0)	0.066
<11 g/dl	32	26 (81.3)		24 (75.0)	
LDH level					
≥305 IU/liter	53	42 (79.2)	0.055	36 (67.9)	0.035
<305 IU/liter	105	95 (90.5)		87 (82.9)	

LDH, lactate dehydrogenase.

Table II. Results of Multivariate Logistic Regression Analysis

Demographic variables	Survival at 8 weeks			Survival at 12 weeks		
	Coefficient	95% CI	*P* value	Coefficient	95% CI	*P* value
Number of metastasized organs (1–2/>2)	1.74	0.58–2.90	0.003	1.71	0.68–2.76	0.001
Performance status (0–1/2)	1.41	0.37–2.47	0.008	1.59	0.72–2.49	< 0.001

CI, confidence interval.

Table III. Survival Rates Divided by Performance Status and Number of Metastasized Organs

Demographic variables		Number of patients (%)	Survival rate at 8 weeks		Survival rate at 12 weeks	
Performance status	Metastatic organs		% (Number)	95% CI	% (Number)	95% CI
0–1	1–2	105 (66.4)	92.4 (97)	88–98	87.6 (92)	81–94
	>2	18 (11.4)	77.8 (14)	55–97	61.1 (11)	39–84
2	1–2	32 (20.3)	81.3 (26)	68–95	62.5 (20)	46–79
	>2	3 (1.9)	0.0 (0)	0–71	0.0 (0)	0–71

CI, confidence interval.

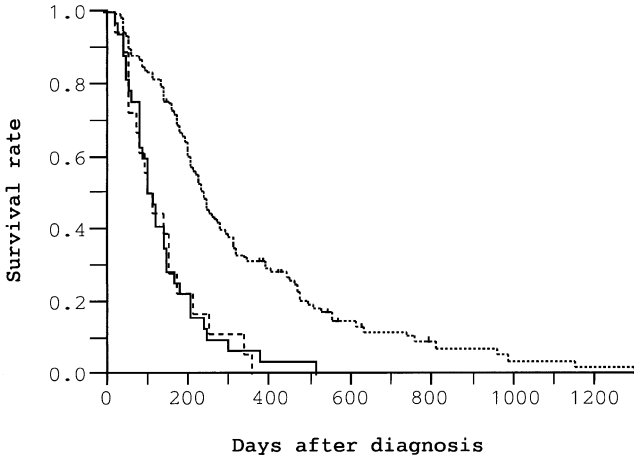

Fig. 1. Kaplan-Meier plots of survival of patients with metastatic non-small cell lung cancer, divided by performance status and number of metastatic organs. Fine dotted line (·····), patients with performance status under 2 and less than 3 metastatic organs; solid line (——), patients with performance status of 2 and less than 3 metastatic organs; coarse dotted line (----), patients with performance status under 2 and more than 2 metastatic organs.

Since elderly patients are generally excluded from clinical trials of chemotherapy, we also analyzed data from which patients over 75 years had been excluded, and again confirmed the importance of these two factors. According to the results of this study, other factors considered significant for usual overall survival were not important for 8- or 12-week survival of our patients. Moreover, it should be mentioned that, even if investigators exclude patients who meet neither of the two conditions from clinical trials, they would miss only a few patients (2%). In the current analysis, the survival rate of patients who met only one of the two conditions was around 80% at 8 weeks, and 62% at 12 weeks. We do not suggest that those patients who meet only one of the two conditions would be always candidates for trials of chemotherapy. Whether or not those patients should be included in a trial depends on the purpose of the trial. If the results of the present analysis were confirmed with a larger population or by prospective studies, this information would help physicians to decide whether to encourage their patients to enter chemotherapy trials or not.

Generally, patients with a performance status of 2 are "possible" candidates for a clinical chemotherapy trial, as stated by Ihde[10] and Shepherd.[11] This restriction is partly explained by the results of the study conducted by the Eastern Cooperative Oncology Group (ECOG). In that study, the response rate and treatment tolerance in patients with a performance status of 2 were lower among fully ambulatory patients.[12] The current study also suggested that patients with a performance status of 2 and with more than 2 metastasized organs might be unsuitable for entry into a clinical trial of chemotherapy, though our sample number was very small (3 patients). However, it might be possible for patients with a performance status of 2 to enter clinical chemotherapy trials when the number of metastasized organs is under 3, because the survival rates

in those patients were 81% and 63% at 8 and 12 weeks, respectively, in this analysis.

Some investigators might feel that a criterion of performance status would be sufficient to select the patients for clinical trials of chemotherapy and that a statement of the minimum life expectancy would be unnecessary. Among the patients with a performance status of 0 or 1, the patients with more than 2 metastasized organs have a significantly lower 12-week survival rate (61%) compared with those having less than 3 metastasized organs (88%, $P=0.005$, Table III). Thus, we consider that the number of organs with metastases should be an important criterion to stratify the prognosis of patients entered into trials. We recommend abandonment of the rather vague criterion "a minimum life expectancy of 8 or 12 weeks" in the eligibility criteria for clinical trials of chemotherapy. Instead, a more objective criterion should be adopted to improve the safety and reproducibility of clinical studies.

ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare of Japan.

(Received October 19, 1998/Revised November 27, 1998/ Accepted December 4, 1998)

REFERENCES

1) Mountain, C. F. Revisions in the international system for staging lung cancer. *Chest*, **111**, 1710–1717 (1997).
2) O'Connell, J. P., Kris, M. G., Gralla, R. J., Groshen, S., Trust, A., Fiore, J. J., Kelsen, D. P., Heelan, R. T. and Golbey, R. B. Frequency and prognostic importance of pretreatment clinical characteristics in patients with advanced non-small-cell lung cancer treated with combination chemotherapy. *J. Clin. Oncol.*, **4**, 1604–1614 (1986).
3) Sørensen, J. B., Badsberg, J. H. and Olsen, J. Prognostic factors in inoperable adenocarcinoma of the lung: a multivariate regression analysis of 259 patients. *Cancer Res.*, **49**, 5748–5754 (1989).
4) Albain, K. S., Crowley, J. J., LeBlanc, M. and Livingston, R. B. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. *J. Clin. Oncol.*, **9**, 1618–1626 (1991).
5) Shinkai, T., Eguchi, K., Sasaki, Y., Tamura, T., Ohe, Y., Kojima, A., Oshita, F., Miya, T., Okamoto, H., Iemura, K. and Saijo, N. A prognostic-factor risk index in advanced non-small-cell lung cancer treated with cisplatin-containing combination chemotherapy. *Cancer Chemother. Pharmacol.*, **30**, 1–6 (1992).
6) Finkelstein, D. M., Ettinger, D. S. and Ruckdeschel, J. C. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. *J. Clin. Oncol.*, **4**, 702–709 (1986).
7) Paesmans, M., Sculier, J. P., Libert, P., Bureau, G., Dabouis, G., Thiriaux, J., Michel, J., Van Cutsem, O., Sergysels, R., Mommen, P. and Klastersky, J. Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European Lung Cancer Working Party. *J. Clin. Oncol.*, **13**, 1221–1230 (1995).
8) Leventhal, B. G. and Wittes, R. E. Phase I trials. *In* "Research Methods in Clinical Oncology," pp. 41–59 (1988). Raven Press, New York.
9) Evans, C. and McCarthy, M. Prognostic uncertainty in terminal care: can the Karnofsky index help? *Lancet*, **1**, 1204–1206 (1985).
10) Ihde, D. C. Chemotherapy of lung cancer. *N. Engl. J. Med.*, **327**, 1434–1441 (1992).
11) Shepherd, F. A. Treatment of advanced non-small cell lung cancer. *Semin. Oncol.*, **21**, 7–18 (1994).
12) Ruckdeschel, J. C., Finkelstein, D. M., Ettinger, D. S., Creech, R. H., Mason, B. A. and Vogl, S. A randomized trial of the four most active regimens for metastatic non-small-cell lung cancer. *J. Clin. Oncol.*, **4**, 14–22 (1986).