Comparative Chemotherapeutic Efficacy in Non-small Cell Lung Cancer Patients with Postoperative Recurrence and Stage IV Disease

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Background: Whether chemotherapy would be equally effective in non-small cell lung cancer patients with stage IV disease (group A) and postoperative recurrence (group B) remains unclear.

Patients and Methods: In a total of 642 non-small cell lung cancer patients with distant metastases treated by chemotherapy, the baseline patient characteristics, responses to chemotherapy and survival were compared between group A ($n = 480$) and group B ($n = 162$).

Results: Adenocarcinoma was the predominant histologic type, accounting for 78% of the patients in group A and 90% of the patients in group B ($p < 0.001$). Bone and brain metastases were more common in group A ($p = 0.034$ and $p = 0.014$, respectively), although pulmonary metastases were more common in group B ($p < 0.001$). The chemotherapy regimens used for the treatment did not differ between groups A and B. The response rates in group A and group B were 32 and 33%, respectively ($p = 0.65$). In contrast, the median progression-free survival (5.5 versus 4.2 months, $p = 0.0065$) and overall survival (21.3 versus 13.3 months, $p < 0.001$) were better in group B than in group A.

Conclusion: Survival was superior in patients with postoperative recurrence than in those with stage IV disease, although the two groups showed comparable responses to chemotherapy.

Key Words: Chemotherapy, Non-small cell lung cancer, Postoperative recurrence, Stage IV disease.

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Until now, non-small cell lung cancer (NSCLC) patients showing disease recurrence after surgery for the primary lesion have been treated with systemic chemotherapy or supportive care alone, in accordance with the treatment offered for patients with stage IV disease,[1] although there have been no comparative studies specifically conducted on these patients. Furthermore, clinical trials conducted to evaluate the efficacy of chemotherapy have, in most cases, included patients with postoperative recurrence as well as those with stage IV disease. However, whether chemotherapy would be equally effective in the two groups of patients remains unclear. The objectives of this retrospective study were to compare the patient characteristics, responses to chemotherapy, and survival between these two patient groups.

PATIENTS AND METHODS

Patient Selection

Patients were retrospectively selected for this study according to the following criteria (1): a histologic or cytologic diagnosis of NSCLC (2); presence of distant metastases at the time of the initial diagnosis (stage IV disease) or postoperative recurrence (3); no prior chemotherapy; and (4) received chemotherapy at the National Cancer Center Hospital between December 2000 and June 2006. Patients were excluded if they had only postoperative local recurrence without distant metastases. All patients underwent systematic evaluation and standardized staging procedures before the start of systemic treatment. Clinical stage was assigned based on the results of physical examination, chest radiography, computed tomography scans of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, and bone scintigraphy. The histologic classification of the tumor was based on the criteria of the World Health Organization.[2]

Data Collection and Statistical Analyses

Patients' baseline characteristics, including age, sex, performance status, histology, site of distant metastases, number of distant metastases, and chemotherapy regimens were obtained retrospectively from the medical charts. Measurable lesions and objective tumor responses were defined according to Response Evaluation Criteria in Solid Tumors (RECIST).[3] All pretreatment and treatment parameters were compared between the two groups, that is, the group with stage IV disease (group A) and the group with postoperative recurrence (group B). χ^2 and Mann-Whitney tests were used to evaluate the differences in categorical and continuous variables, respectively, between the two groups. The overall and progression-free survivals were evaluated using the

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Kaplan-Meier method and logrank test. Cox proportional hazards models were used to adjust for potential confounding factors.[4] All analyses were performed using the Dr. SPSS II 11.0 for Windows software (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Characteristics

A total of 642 patients met the eligibility criteria for this study. Of these, 480 patients (75%) had stage IV disease (group A) and 162 (25%) had postoperative recurrence (group B). In group B, pathologic stage I, stage II, stage III, and stage IV disease was noted in 49 (30%), 32 (20%), 76 (47%), and 5 (3%) patients, respectively. The median interval from the day of the operation for the primary disease and the first day of chemotherapy was 22.2 months. Baseline characteristics stratified by the groups are summarized in Table 1. Sex distribution did not differ between the two groups, but the median age was 2.5 years higher in group B. Adenocarcinoma was the predominant histologic type, accounting for 78% of patients in group A and 90% of patients in group B ($p < 0.001$). The predominant sites of metastases differed between the two groups; bone and brain metastases were more common in group A ($p = 0.034$ and $p = 0.014$, respectively), although pulmonary metastases were more common in group B ($p < 0.001$). Chemotherapy regimens used for first-line chemotherapy did not differ between the two groups. Platinum-based chemotherapy, nonplatinum doublet chemotherapy, mono-chemotherapy with a third-generation cytotoxic agent, and epidermal growth factor receptor tyrosine kinase inhibitors were administered in 360 (75%), 4 (1%), 29 (6%), and 87 (18%) patients in group A, respectively, and 109 (67%), 5 (3%), 18 (11%), and 30 (19%) patients in group B, respectively.

Responses and Survival

A total of 472 (98%) of the 480 patients in group A, but only 100 (62%) of the 162 patients in group B, had measurable lesions ($p < 0.001$, Table 2). Among patients with measurable lesions, responses to chemotherapy were comparable between the patients of group A and group B (Table 2). Progression-free survival, however, was superior in group B

TABLE 1. Patient Characteristics

	Group A[a] (n = 480)		Group B[a] (n = 162)		
	n	(%)	n	(%)	p
Sex					0.23
Female	173	(36.0)	67	(41.4)	
Male	307	(64.0)	95	(58.6)	
Age median (range)	60	(24–86)	62.5	(32–81)	0.004
Histology					0.001
Adenocarcinoma	375	(78.1)	145	(89.5)	
Nonadenocarcinoma	105	(21.9)	17	(10.5)	
Performance status					0.23
0	137	(28.5)	60	(37.0)	
1	316	(65.8)	95	(58.6)	
2	22	(4.6)	6	(3.7)	
3	5	(1.0)	4	(0.6)	
No. of metastatic organs					0.96
1	303	(63.1)	104	(64.2)	
2	125	(26.0)	39	(24.1)	
3	35	(7.3)	13	(8.0)	
4–6	17	(3.5)	6	(3.7)	
Metastatic sites					
Bone					0.034
No	287	(59.8)	112	(69.1)	
Yes	193	(40.2)	50	(30.9)	
Brain					0.014
No	347	(72.3)	133	(82.1)	
Yes	133	(27.7)	29	(17.9)	
Lung					<0.001
No	256	(53.3)	57	(35.2)	
Yes	224	(46.7)	105	(64.8)	
Liver					0.26
No	423	(88.1)	148	(91.4)	
Yes	57	(11.9)	14	(8.6)	

[a] Group A: patients with stage IV disease; group B: patients with postoperative recurrence.

TABLE 2. Objective Responses to Chemotherapy

	Group A		Group B		
	n	(%)	n	(%)	p
Measurable lesions (n = 642)					<0.001
Yes	472	(98.3)	100	(61.7)	
No	8	(1.7)	62	(38.3)	
Objective responses in patients with measurable lesions (n = 572)					0.65
Complete response	5	(1.1)	1	(1.0)	
Partial response	145	(30.7)	32	(32.0)	
Stable disease	170	(36.0)	29	(29.0)	
Progressive disease	100	(21.2)	23	(23.0)	
Not evaluable[a]	52	(11.0)	15	(15.0)	

[a] In these patients, chemotherapy was discontinued early because of toxicity. Group A: patients with stage IV disease; group B: patients with postoperative recurrence.

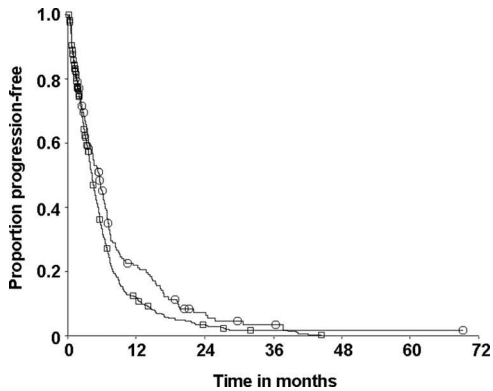

FIGURE 1. Progression-free survival in patients with stage IV disease (open square, n = 480) and in those with postoperative recurrence (open circle, n = 162).

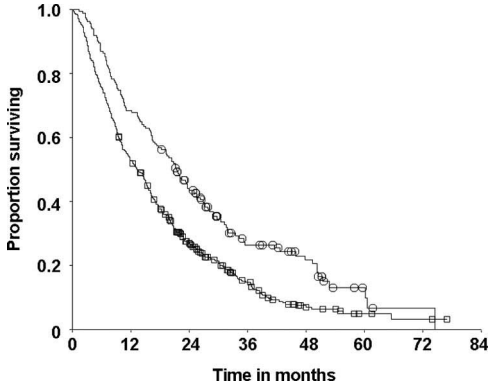

FIGURE 2. Overall survival in patients with stage IV disease (open square, $n = 480$) and in those with postoperative recurrence (open circle, $n = 162$).

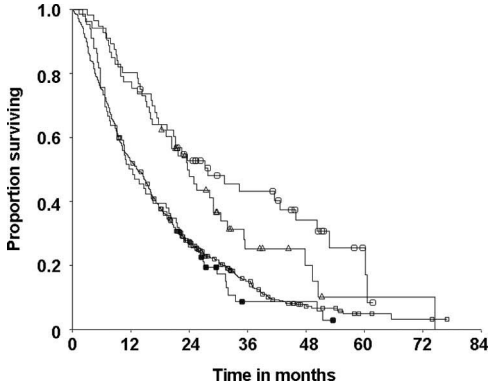

FIGURE 3. Overall survival in patients with stage IV disease (open square, $n = 480$) and in those with postoperative recurrence according to the interval between the day of the operation and the first day of chemotherapy. The interval had a significant impact on the survival from the start of chemotherapy. Open circle ($n = 54$), interval of 30.0 months or longer; open triangle ($n = 53$), interval of 15.0 to 29.9 months, and closed circle ($n = 55$), interval shorter than 15.0 months.

than in group A (5.5 versus 4.2 months, $p = 0.0065$, Figure 1). Overall survival was also superior in group B than in group A (21.3 versus 13.3 months, $p < 0.001$, Figure 2). The interval between the day of operation and the first day of chemotherapy had a significant impact on the survival from the start of chemotherapy. Median survival time (MST) from the start of chemotherapy was 23.6 and 27.8 months, respectively, in patients in whom the interval was 15.0 to 29.9 months and 30 months or longer, respectively. In contrast, the median survival time from the start of chemotherapy was only 11.7 months in the patients in whom the interval was less than 15.0 months ($p < 0.001$), which was comparable with that in patients with stage IV disease (group A; 13.4 months) (Figure 3). Pathologic stage at the time of surgery had no impact on the overall survival of the patients in group B. Other known prognostic factors including male sex, a poor performance status, a large number of metastatic organs, and the presence of bone metastasis were associated with poor patient survival (Table 3), whereas brain metastasis had no

TABLE 3. Factors Associated with Overall Survival

	Hazard Ratio (95% Confidence Interval)			
	Univariate Analysis	*p*	Multivariate Analysis	*p*
Sex				<0.001
Female	1		1	
Male	1.56 (1.30–1.86)	<0.001	1.58 (1.32–1.90)	
Performance status				
0	1		1	
1	1.43 (1.19–1.74)	<0.001	1.31 (1.08–1.58)	0.007
2–3	2.76 (1.88–4.05)	<0.001	2.49 (1.67–3.70)	<0.001
Number of metastatic organs[a]	1.25 (1.13–1.37)	<0.001	1.26 (1.12–1.42)	<0.001
Bone metastasis				0.91
No	1		1	
Yes	1.45 (1.22–1.73)	<0.001	1.01 (0.82–1.25)	
Pulmonary metastasis				0.005
No	1		1	
Yes	0.72 (0.61–0.85)	<0.001	0.76 (0.63–0.92)	
Group				<0.001
A	1		1	
B	0.63 (0.51–0.77)	<0.001	0.66 (0.54–0.81)	

[a] With an increment of one. Group A: patients with stage IV disease; group B: patients with postoperative recurrence.

impact on survival (hazard ratio, 1.11; 95% confidence interval, 0.91–1.35; $p = 0.30$) and pulmonary metastasis was associated with a better survival (Table 3). Multivariate analysis using a Cox's proportional hazard model showed that patients in group B had a better prognosis than those in group A with a hazard ratio of 0.66 (95% confidence interval, 0.54–0.81, $p < 0.001$) (Table 3).

DISCUSSION

This study revealed different characteristics of patients with postoperative recurrence who received systemic chemotherapy for tumor recurrence in comparison with those of patients with stage IV disease among NSCLC patients. Considering the interval between the operation and chemotherapy, the median value of which was 22 months, it is understandable that the median age of patients with postoperative recurrence was 2 years higher than that of the patients with stage IV disease. The percentage of patients with adenocarcinoma was higher in the group of patients with postoperative recurrence, probably because recurrence after surgical resection may be more common in patients with adenocarcinoma than in patients with squamous cell carcinoma. This is consistent with a previous report that squamous cell histology was associated with a good prognosis among patients with stage IIIA disease.[5] Recent large-scale randomized trials in previously treated advanced NSCLC patients have shown that epidermal growth factor receptor tyrosine kinase inhibitors are more effective against adenocarcinomas (with response rates of 12–13%) than against nonadenocarcinomas (with response rates of no more than 5%).[6,7] In the current study, these agents were administered as a first-line chemotherapy in

18% of the patients with stage IV disease and in 19% of the patients with postoperative recurrence; no data regarding the use of these agents in second-line or subsequent chemotherapy regimens was available. Thus, the use of this class of agents may have influenced the survival difference between the patients with stage IV disease and those with postoperative recurrence. Brain and bone metastases were significantly less common in patients with postoperative recurrence in this study. These patients may have been less frequently referred to medical oncologists, possibly because of a poor performance status and could therefore be suitable candidates for palliative radiotherapy. However, pulmonary metastases were significantly more common in the group with postoperative recurrence, possibly because these patients can only be treated with systemic chemotherapy.

Thirty-eight percent of patients with postoperative recurrence had no measurable lesions. Many of these patients had multiple small pulmonary metastases, but no evidence of recurrence at other sites. Excluding these patients, evaluation of the response to chemotherapy revealed no difference in percentages of patients showing complete and partial responses between the two groups. Thus, it is reasonable to include patients with postoperative recurrence in studies in which the primary end point is the response rate, such as conventional phase II studies, as long as they have measurable disease.

Patient survival was significantly superior in patients with postoperative recurrence compared with those with stage IV disease in this study, with a hazard ratio of 0.66 ($p < 0.001$). To our knowledge, there are no such data in the medical literature except one report, which showed that prior lung surgery may have been associated with a better prognosis, with a hazard ratio of 0.86.[8] This reported difference, however, was much smaller than that found in this study. Patients with postoperative recurrence constitute a heterogeneous group, and patients with a relatively better prognosis tended to be included in this group in the current study. The disease-free interval between the operation and recurrence has been reported as a prognostic factor.[9] In this study, patients with an interval from the operation to the start of postrecurrence chemotherapy of less than 15.0 months had a survival rate as poor as that in patients with stage IV disease. These patients who showed relatively early recurrence accounted for only one-third of all the patients with postoperative recurrence in this study. In conclusion, the NSCLC patients with postoperative recurrence had characteristics different from those with stage IV disease in this study, but the two groups showed comparable responses to chemotherapy. Survival, both progression-free and overall, was superior in those with postoperative recurrence as compared with those with stage IV disease, especially those having a postoperative disease-free interval of more than 15 months.

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