

Long-term Survivors after Chemotherapy in Advanced Non-small Cell Lung Cancer

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Abstract. *Background: Chemotherapy is considered to have a marginal impact on survival. The purpose of this study was to evaluate the rate of long-term survival in patients treated with chemotherapy for advanced non-small cell lung cancer (NSCLC). Patients and Methods: The case records of 109 patients with NSCLC treated with chemotherapy from March 1998 to March 2007 were reviewed. Results: Fourteen (12.8%) and seven (6.4%) patients survived for more than two or three years, respectively. All of the 14 patients had performance status (PS) 0 or 1, and they were given a platinum-containing chemotherapy as initial treatment. By means of univariate analysis, good PS and gefitinib therapy were proved to be good prognostic factors. With Cox's model analysis, these two variables were confirmed as significant determinants of survival. Conclusion: A small but definite proportion of patients with locally-advanced and metastatic NSCLC might potentially survive for more than 2 years with appropriate chemotherapy.*

Lung cancer is one of the most common causes of cancer-related death. Of lung carcinomas, non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases, presenting as locally advanced disease in approximately 25-30% of cases and as metastatic disease in approximately 40-50% of cases (1). Although surgery is the standard treatment, unfortunately for the majority of patients with NSCLC, the disease is diagnosed at a stage too advanced to allow surgical treatment. Platinum-containing regimens have constituted the backbone of chemotherapy trials in many kinds of cancer; however, NSCLC is generally chemo-resistant (2-4). Some studies

have demonstrated a survival benefit from chemotherapy for advanced NSCLC, but chemotherapy is considered to have a marginal impact on survival (5-7). The purpose of this study was to evaluate the rate of long-term survival in 109 patients, treated with chemotherapy for advanced NSCLC, as conducted by our division, and to determine whether or not there were any specific factors to discriminate long- and short-term survivors.

Patients and Methods

Patients. One hundred and nine consecutive, unselected and previously untreated NSCLC patients, who were admitted to our division between March 1998 and March 2007, were included in this study. Staging was performed for all the patients according to the TNM classification (8), before treatment, using chest CT, brain MRI and bone scan as well as ultrasonography and/or CT of the abdomen, and they were diagnosed as having stage IIIB-IV disease. Among them were 37 Stage IIIB and 72 Stage IV cases. The histological types were 84 adenocarcinoma, 15 squamous cell carcinoma and 10 large cell carcinoma as defined by the WHO classification (9). Table I shows the chemotherapy regimens administered to the patients.

Statistical analysis. The Mann-Whitney U-test was applied to elucidate the difference between two groups. Survival was recorded from the first day of treatment to the date of death or last follow-up, and the survival curves were calculated according to the method of Kaplan-Meier (10). Univariate survival analysis was calculated using the generalized Wilcoxon test and Cox regression was used to simultaneously evaluate various prognostic factors (11). Values of $p < 0.05$ were considered significant.

Results

Long-term survivors after chemotherapy. Out of the 109 patients, 14 (12.8%) and 7 (6.4%) survived for more than two or three years, respectively. The median survival time for the 14 patients was 36 months, ranging from 24 to 56 months. Table II shows the individual characteristics and survival status of the 14 patients. Of the 14 two- or more-year survivors, all were performance status (PS) 0 or 1, and they were given a platinum-containing chemotherapy as the

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Table I. First line chemotherapy regimens administrated to 109 patients with NSCLC.

Regimens	No. of patients
Cisplatin-containing	36
CDDP+VNR	15
CDDP+VDS	13
CDDP+CPT-11	4
CDDP+DTX	2
CDDP+GEM	1
CDDP+VP-16	1
Carboplatin-containing	58
CBDCA+PTX	43
CBDCA+VDS	6
CBDCA+DTX	5
CBDCA+VP-16	2
CBDCA+VNR	1
CBDCA+GEM	1
Gefitinib	13
DTX	1
VNR	1

CDDP: cisplatin; VNR: vinorelbine; VDS: vindesine; DTX: docetaxel; GEM: gemcitabine; PTX: paclitaxel; CBDCA: carboplatin; CPT-11: irinotecan; VP-16: etoposide.

initial treatment. Two of these patients received concurrent or sequential chest irradiation and 1 patient underwent a surgical resection after initial chemotherapy. Eight out of the 14 patients received gefitinib as the second or third line chemotherapy.

Prognostic factors. The prognostic factors were evaluated by univariate analysis and the distribution of patient prognostic factors is shown in Table III. Good performance status and gefitinib therapy were shown to be good prognostic factors. To further clarify the independent prognostic importance of the categories, Cox's proportional hazard model was used for analysis. For each variable, the proportional hazard assumption was tested graphically and with this analysis, these two variables were confirmed as significant determinants of survival (Table III).

Thirty-six and 58 patients received cisplatin-containing chemotherapy or carboplatin-containing chemotherapy, respectively. Fifteen patients received non-platinum chemotherapy. The median age of the cisplatin-treated group was 57 years (range: 32-70 years), and that of the carboplatin-treated group was 65 years (range: 34-81 years). There was a statistically significant difference in age between the two groups ($p=0.001$). In addition, there was a difference in PS between the two groups ($p=0.013$). In the cisplatin-treated group, the response rate was 25.0%, the median survival time (MST) was 9 months and 2- and 3-year

survival was 19.4% and 13.9%, respectively. In the carboplatin-treated group, the response rate was 24.1%, the MST was 7 months and 2- and 3-year survival was 12.1% and 3.4%, respectively.

Discussion

Some previous studies have reported long-term survivors among unresectable NSCLC (12-18). In these studies, patients with locally advanced and metastatic disease were included, and they were mainly treated initially with chemotherapy followed by other treatments (12-18). These studies showed that only 10-21% and 4-6% of NSCLC patients with locally advanced and metastatic disease survived for more than two years, respectively (12-15, 19-22). Recently, Okamoto *et al.* have reported that 17 (7.7%) of 222 NSCLC patients with metastatic disease survived for more than 2 years (23). In the present study, 6 (16.2%) out of the 37 locally advanced and 8 (11.1%) out of the 72 metastatic NSCLC patients survived for more than 2 years. Our results confirmed that adequate treatment plays an important role in the long-term survival of locally advanced and metastatic NSCLC and an appropriate treatment strategy must be considered for some patients in good clinical condition.

The great majority of published studies concerning prognostic factors for NSCLC have included patients in clinical trials where a poor performance status and significant weight loss were the usual exclusion criteria. Such selected patients are probably different from most of those with NSCLC who are seen in daily clinical practice. For this population, we need to know not only the prognostic power of individual factors with respect to prediction of disease free and overall survival, but also their possible relationship to response to chemotherapy, in order to select adequate treatment for each patient. In a previous study (16) of NSCLC patients, who were treated in our division between 1987 and 1996, 7.2% and 3.6% of the patients survived for more than 2 or 3 years, respectively. The ratio of 2-year survivors in the present study (12.8%) tended to be higher than that in our previous study (7.2%) ($p=0.1079$). In our previous study, all of the patients who survived for more than 2 years had received cisplatin-containing regimens. In the present study, 8 out of the 14 patients received gefitinib as second or third line chemotherapy. Good performance status and gefitinib therapy were identified as significant predicting factors for survival. In addition to this, our results confirmed that a small, but definite proportion of the patients with locally-advanced and metastatic NSCLC might potentially survive for more than 2 years with appropriate treatment including platinum-containing chemotherapy.

Table II. Individual characteristics of the 14 patients with 2 or more years survival.

No.	Survival (months)	Age	Gender	PS	Stage	Histology	Chemotherapy regimen	Response	Further treatment
1	24	69	F	0	3B	AD	CBDCA+PTX	PR	GEM+VNR
2	27	75	F	1	4	AD	CBDCA+PTX	PR	Gefitinib
3	30	63	M	1	3B	AD	CBDCA+PTX	PD	GEM+VNR,Gefitinib
4	30	60	F	1	4	AD	CDDP+VNR	SD	Gefitinib
5	31	65	M	1	4	AD	CDDP+VNR	SD	Gefitinib
6	32	61	M	1	3B	AD	CBDCA+VDS+TRT	PR	-
7	35	58	M	1	4	AD	CBDCA+PTX	PR	Gefitinib
8	36	60	M	1	3B	AD	CBDCA+PTX	PR	TS-1
9	36	59	M	0	3B	AD	CDDP+VNR	PD	Gefitinib
10	36	68	M	1	3B	AD	CDDP+VNR	SD	Gefitinib
11	45	56	F	0	4	AD	CDDP+VNR	SD	Gefitinib
12	46	59	F	0	4	AD	CDDP+DTX	SD	-
13	56	70	M	1	3B	SQ	CBDCA+VDS+TRT	SD	-
14	56	45	M	0	4	AD	CDDP+VNR	PR	-

PS: performance status; AD: adenocarcinoma; SQ: squamous cell carcinoma; CBDCA: carboplatin; PTX: paclitaxel; CDDP: cisplatin; VNR: vinorelbine; VDS: vindesine; TRT: thoracic radiotherapy; DTX: docetaxel; GEM: gemcitabine.

In the present study, the NSCLC patients managed to tolerate cisplatin-containing chemotherapy, however, since aggressive hydration is sometimes problematic, carboplatin was considered to be a substitute for cisplatin without apparent loss of therapeutic efficacy. Very recently, Jiang *et al.* have reported that cisplatin-based regimens had a higher overall response rate as compared with carboplatin-based regimens, based on a meta-analysis of randomized controlled trials comparing cisplatin-based to carboplatin-based chemotherapy in advanced NSCLC (24). However there was no survival advantage in the cisplatin group, and they concluded that the toxicity profile may be an important factor in deciding between cisplatin-based or carboplatin-based regimens (24). Our carboplatin-containing regimens seem to be an appropriate approach in NSCLC patients, in view of its impact on both response rate and overall survival.

Our results with a limited number of patients were based on neither a prospective nor a randomized controlled study. However, reporting the management of unselected groups of patients has some clinical importance for the treatment of future patients, because up to now clinical trials in NSCLC have usually included only "selected" patients, who are not representative of the usual NSCLC patients.

Out of the 109 patients, 14 (12.8%) and 7 (6.4%) survived for more than two or three years respectively, all were of good performance status and were given a platinum-containing chemotherapy as an initial treatment. Good performance status and gefitinib therapy were shown to be good prognostic factors. In addition to this, our results confirmed that a small, but definite proportion of patients with locally-advanced and metastatic NSCLC might

Table III. Uni- and multi-variate analyses of prognostic factors.

Factor	Uni-variate analysis (generalized Wilcoxon test)		Multi-variate analysis (Cox's proportional hazard model)		
	p-value	odd-ratio	95%CI	p-value	
Age(65≥, >65)	0.758	0.75	0.39-1.44	0.389	
Gender	0.618	1.53	0.45-3.09	0.240	
Pathology(AD,non-AD)	0.876	1.07	0.50-2.27	0.861	
PS(0-1,2-4)	0.001	4.72	2.29-9.70	0.001	
Stage(IIIB,IV)	0.460	0.90	0.48-1.67	0.735	
Chemotherapy (CDDP-containing,others)	0.357	0.66	0.36-1.21	0.181	
Gefitinib	0.021	2.29	1.15-4.56	0.018	
Thoracic irradiation	0.711	1.70	0.76-3.84	0.199	

AD: adenocarcinoma; PS: performance status; CDDP: cisplatin.

potentially survive for more than 2 years with appropriate treatment including platinum-containing chemotherapy.

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