Similar survival benefits of a good response and stable disease to platinum-based chemotherapy in non-small cell lung cancer

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Abstract. The present study aimed to evaluate the similar survival benefits of a good response [complete response or partial response (CR/PR)] and stable disease (SD) to chemotherapy in non-small cell lung cancer (NSCLC) patients in clinical practice. All 322 patients who were treated between 1999 and 2012 with first-line platinum-based chemotherapy were retrospectively analyzed. Tumor responses were classified according to the response evaluation criteria for solid tumors. A total of 67 (20.8%) patients experienced CR/PR and 165 (51.2%) achieved SD. There was no difference in progression-free survival between the patients with CR/PR and those with SD (P=0.347). There was also no difference between the two groups with regard to overall survival time (P=0.878). In multivariate analysis, disease-control (more than SD) was one of the favorable prognostic factors. In clinical practice, a survival benefit would be provided not only for the patients who have good response, but also for those with SD.

Introduction

The incidence and mortality rates of lung cancer have increased globally during the last few decades (1,2). The majority of cases of lung cancer diagnosed were non-small cell lung cancer (NSCLC), and ~40% of patients with NSCLC are affected by advanced diseases (3). For patients with advanced NSCLC with a good performance status, systemic chemotherapy is the standard therapy at present. The first-line treatment for such patients is platinum-based chemotherapy, which improves symptom control, quality of life and survival as compared with best supportive care (4). A good response [complete response or partial response (CR/PR)] to chemotherapy has typically been equated with the clinical benefit of increased survival (5), but only 20-30% of patients achieve a good response in previous clinical trials, while 40-50% maintain a stable disease (SD) status (6-8). Certain previous studies reported that an initial good response and stable disease indicate similar survival benefits for chemotherapeutical patients with advanced NSCLC (9,10). The present retrospective study was undertaken to evaluate the similar survival benefits of a good response and stable disease to platinum-based chemotherapy in previously untreated NSCLC patients.

Patients and methods

Patients. The patients enrolled in the present study were those consecutively diagnosed with NSCLC and treated with platinum-based chemotherapy as first-line treatment at the University of Tsukuba Hospital and Tsukuba Medical Center Hospital (both Tsukuba, Ibaraki, Japan) between January 1999 and December 2012. All the patients were histologically/cytologically confirmed as presenting with NSCLC and unresectable advanced disease. The histopathological diagnosis was defined by the World Health Organization classification (11), and patients were staged according to the Union for International Cancer Control tumor-node-metastasis system (12).

Treatment and response. Enrolled patients received at least one cycle of cisplatin- or carboplatin-based chemotherapy. The clinical, pathological and radiological data, and the follow-up information obtained until May 2013 were retrospectively reviewed. The patient characteristics and efficacy were evaluated using patient data extracted from the database. Tumor responses were classified as a CR, PR, SD, progressive disease (PD) or not evaluable (NE), according to the response evaluation criteria for solid tumors (RECIST) version 1.1 (13). This observational study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor and Welfare of Japan.

The progression-free survival (PFS) time of each patient was calculated from the day that chemotherapy was commenced until disease progression. Overall survival (OS) time was

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calculated from the day that chemotherapy was commenced until mortality or the latest follow-up of the patient.

Statistical analysis. The survival rate was analyzed by the Kaplan-Meier method, and comparisons were performed using the log-rank test in univariate analysis. Significant variables identified in the univariate analysis were included in the multivariate survival analysis using Cox proportional hazards model to study the effects of clinicopathological factors on survival. P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using StatView software for Windows, version 5.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patients. Between January 1999 and December 2012, 322 patients were diagnosed with advanced NSCLC and received platinum-based chemotherapy at two hospitals. The median follow-up period was 10.2 months (range, 0.7-134.0 months). Table I shows the patient characteristics. Of the 322 patients, 234 were male, and the median age was 64 years (range, 21-88 years). In total, 85 patients were never-smokers. With regard to performance status (PS), 258 patients exhibited a PS of 0-1 and 64 exhibited a PS of 2-4. Overall, 33 patients presented with stage IIIA-B disease and 289 patients with stage IV. Of the 322 NSCLC cases, 246 (76.4%) were adenocarcinoma, 62 (19.3%) were squamous cell carcinoma, 11 (3.4%) were large cell carcinoma, and 3 (0.9%) were other types. Epidermal growth factor receptor (EGFR) mutation positivity was found in 19 patients, while 69 patients were negative for the mutation and 234 patients were not evaluated for EGFR. The chemotherapy regimens used are presented in Table II; 105 (32.6%) patients were administered cisplatin-based chemotherapy, and 217 (67.4%) patients were administered carboplatin-based chemotherapy as first-line treatment. In the platinum-based chemotherapy regimens [carboplatin (area under the serum concentration-time curve, 4-5 mg/ml/min; day 1; 3-4-week cycle) and cisplatin (60-80 mg/m^2; day 1, 3-4-week cycle)], the cytotoxic drugs such as paclitaxel (180-200 mg/m^2; day 1; 3-4-week cycle), doctaxel (60 mg/m^2; day 1; 3-4-week cycle), gemcitabine (1000 mg/m^2; days 1 and 8; 3-4-week cycle) and pemetrexed (500 mg/m^2; day 1; 3-4-week cycle) were administered in 95, 62, 47 and 43 patients, respectively. The median number of cycles of platinum-based chemotherapy was 2 (range, 1-7 cycles), and the median number of cycles of maintenance therapy was 3 (range, 1-12 cycles).

Response/disease control and survival. The median OS time for the 322 patients was 11.7 months. A total of 67 (20.8%) patients were responders (no CR and 67 PR) and 165 (51.2%) patients achieved SD, which amounted to a disease control rate (DCR) of 72.0%. In the 260 patients with non-squamous cell carcinoma, 50 (19.2%) were responders (no CR and 50 PR) and 135 (51.9%) achieved SD, which amounted to a DCR of 71.1%. In the 62 patients with squamous cell carcinoma, 17 (27.4%) were responders (no CR and 17 PR) and 30 (48.4%) patients achieved SD, which amounted to a DCR of 75.8%.

As shown in Fig. 1, the median OS time in the 232 patients with CR/PR or SD was better than that of the 90 patients with PD (14.6 vs. 5.1 months; P<0.001). By contrast, there was no difference in PFS time between the 67 patients with CR/PR and the 165 patients with SD (6.8 vs. 5.5 months; P=0.347) (Fig. 2). There was also no significant difference between patients with CR/PR and those with SD with regard to OS time (15.6 vs. 14.3 months; P=0.878) (Fig. 3).

In the patients with non-squamous cell carcinoma, the median OS time in the patients with CR/PR and SD was better than that in the patients with PD (16.1 vs. 5.2 months; P<0.001). There was no difference in PFS time between the patients with CR/PR and the patients with SD (7.3 vs. 5.7 months; P=0.253). Additionally, there was no significant difference between the patients with CR/PR and those with SD with regard to OS (16.9 vs. 15.1 months; P=0.938).

In the patients with squamous cell carcinoma, the OS time in the patients with CR/PR and SD was better than that in the patients with PD (13.1 vs. 4.8 months; P<0.001). There was no difference in PFS time between the patients with CR/PR and the patients with SD (5.0 vs. 5.1 months; P=0.978). Also, there was no significant difference between the patients with CR/PR and those with SD with regard to OS time (13.1 vs. 13.3 months; P=0.732).

Prognostic factors. Next, the prognostic factors of the 322 NSCLC patients were evaluated. Table III presents the results of the univariate and multivariate analyses. In the

Table I. Characteristics of 322 patients with non-small cell lung cancer who received platinum-based chemotherapy.

Characteristic	Value
Median age (range), years	64 (21-88)
Gender, n (%)	
Male	234 (72.7)
Female	88 (27.3)
Smoking status, n (%)	
Smoker	237 (73.6)
Never-smoker	85 (26.4)
Performance status, n (%)	
0-1	258 (80.1)
2-4	64 (19.9)
Clinical stage, n (%)	
IIIA-B	33 (10.2)
IV	289 (89.8)
Pathology, n (%)	
Adenocarcinoma	246 (76.4)
Squamous cell carcinoma	62 (19.3)
Large cell carcinoma	11 (3.4)
Other	3 (0.9)
EGFR mutation, n (%)	
Positive	19 (5.9)
Negative	69 (21.4)
Not evaluated	234 (72.7)

EGFR, epidermal growth factor receptor.

Table II. Regimens of chemotherapy.

Regimen	Value
Platinum, n (%)	
Cisplatin	105 (32.6)
Carboplatin	217 (67.4)
Combined drugs, n (%)	
Paclitaxel	95 (29.5)
Docetaxel	62 (19.3)
Gemcitabine	47 (14.6)
Pemetrexed	43 (13.4)
Vinorelbine	38 (11.8)
S-1	13 (4.0)
Etoposide	12 (3.7)
Vindesine	11 (3.4)
Bevacizumab	11 (3.4)
Irinotecan	3 (0.9)
Median number of platinum-based chemotherapy cycles (range)	2 (1-7)
Median number of maintenance therapy cycles (range)	3 (1-12)

univariate analysis, the female gender, a good PS (PS of 0-1), never-smoker status, non-squamous cell carcinoma, cisplatin-based chemotherapy, pemetrexed-containing chemotherapy, bevacizumab-containing chemotherapy and disease-controlled patients (CR/PR and SD) were associated with a longer OS time. According to the multivariate Cox proportional hazards model, a good PS (PS of 0-1), never-smoker status, pemetrexed-containing chemotherapy and disease-controlled patients (CR/PR and SD) were favorable prognostic factors.

Discussion

In the present study evaluating daily practice in NSCLC patients, four main results were found. First, in the overall group of NSCLC patients, the DCR (CR/PR and SD rates) was 72.0%, although the response rate that was composed of CR/PR alone was only 20.8%. Second, the OS time was 11.7 months in the overall group of NSCLC patients, and 14.6 months in the disease-controlled patients (patients with CR, PR and SD). Third, the OS time in the disease-controlled patients was longer than that in the patients with PD, but there was no statistical significant difference in the OS time between the patients with CR/PR and those with SD. The same results were observed in the patients with squamous cell lung carcinoma and those with non-squamous cell carcinoma. Fourth, the OS time in the disease-controlled patients treated with platinum and pemetrexed was 21.4 months.

Thus, these results illustrated that prolongation of survival time was associated not with the response rate, but with the disease control rate, and a high response rate may have scarce clinical meaning in daily practice. If a cure would not be achieved, these results implied that it would be

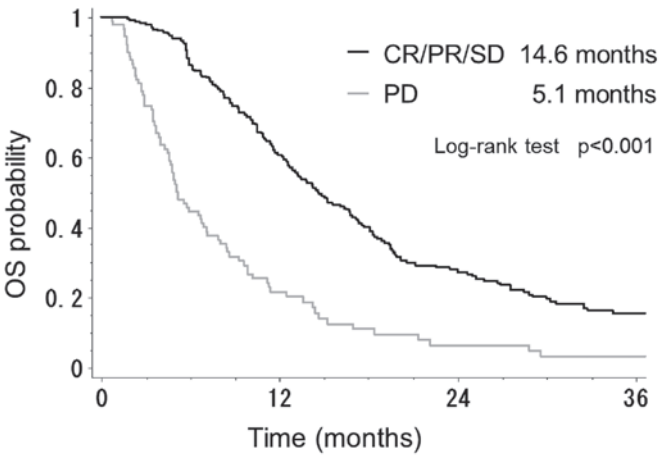

Figure 1. OS in non-small cell lung cancer patients with a CR/PR/SD or PD. Patients with CR/PR/SD had a significantly better prognosis compared with patients with PD (median OS, 14.6 vs. 5.1 months; P<0.001). OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

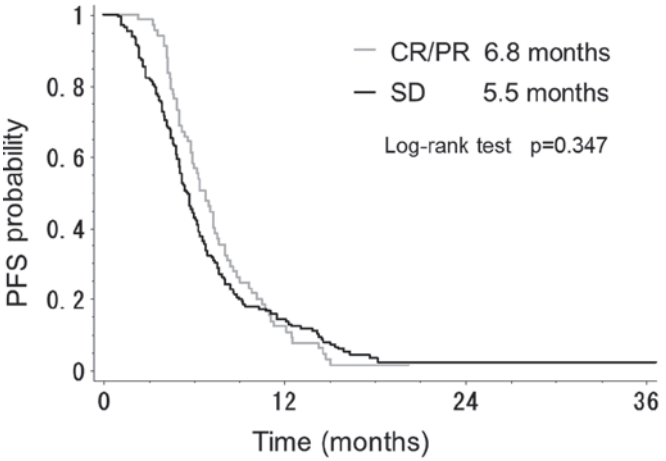

Figure 2. PFS in non-small cell lung cancer patients with CR/PR or SD. No significant difference was identified between the patients with CR/PR and SD (median PFS, 6.8 vs. 5.5 months; P=0.347). PFS, progression-free survival; CR, complete response; PR, partial response; SD, stable disease.

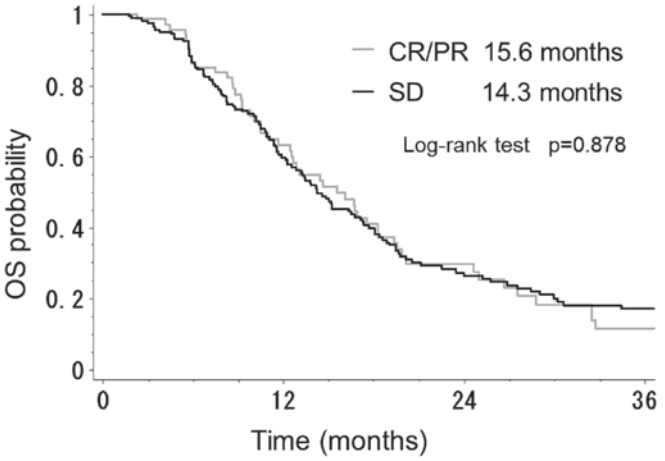

Figure 3. OS in non-small cell lung cancer patients patient with CR/PR or SD. No significant difference was identified between patients with CR/PR and SD (median OS, 15.6 months vs. 14.3 months, P=0.878). OS, overall survival; CR, complete response; PR, partial response; SD, stable disease.

Table III. Prognostic factors of the 322 non-small cell lung cancer patients.

A, Univariate survival analysis (log-rank test)

Prognostic factors	Median OS time, months	P-value
Gender (female/male)	16.7/10.9	<0.001
Age, years (<70/≥70)	11.2/13.3	0.528
PS (0-1/2-4)	13.6/5.8	<0.001
Smoking status (never-smoker/smoker)	18.1/11.0	<0.001
Non-squamous/squamous cell carcinoma	12.3/10.5	0.046
CDDP/CBDCA	13.5/11.4	0.041
PEM (+/-)	21.4/10.2	<0.001
Bevacizumab (+/-)	21.4/11.3	0.004
Maintenance (+/-)	18.1/11.6	0.191
CR+PR/SD+PD	15.6/11.2	0.064
CR+PR+SD/PD	14.6/5.1	<0.001

B, Multivariate analysis (Cox's proportional hazards model)

Prognostic factors	Hazard ratio	95% CI	P-value
Female	0.75	0.52-1.07	0.106
PS 0-1	0.48	0.35-0.66	<0.001
Never-smoker	0.64	0.44-0.93	0.020
Non-squamous cell carcinoma	0.98	0.71-1.36	0.896
CDDP	0.95	0.71-1.27	0.722
PEM	0.47	0.32-0.68	<0.001
Bevacizumab	0.60	0.32-1.14	0.117
CR+PR+SD	0.37	0.28-0.48	<0.001

CDDP, cisplatin; CBDCA, carboplatin; PEM, pemetrexed; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

important not to merely achieve shrinkage of the tumor, but to maintain the patent's condition for a long time without any tumor progression.

In previous studies, there have been various opinions with regard to the survival of patients with SD; certain studies have insisted that patients with SD were associated with a favorable, long OS time compared with those with CR/PR (9,10), and another study described a longer OS time obtained in patients with CR/PR compared with those with SD (14). Lara *et al* (9) suggested that patients who achieved SD at 8 weeks experience a survival time equal to that of PR/CR patients. The study claimed that DCR (CR, PR and SD) is stronger than response (CR/PR alone) in the prediction of the OS time of patients with advanced NSCLC. He *et al* (10) reported that initial CR/PR and SD result in similar PFS and OS times for patients with advanced NSCLC receiving platinum-based chemotherapy. One previous study suggested that SD may be representative of a potential survival benefit of chemotherapy. Therefore, the differentiation between SD and CR/PR may not be of any practical importance (15). By contrast, Coudert *et al* (14) reported that SD after first-line chemotherapy was a significant negative prognostic factor compared with CR/PR. Recently, Mandrekar *et al* (16) indicated that patients with PD experienced worse survival compared with those with non-PD, with a certain degree of separation between the NSCLC categories of SD and CR/PR. Controversy remains with regard to whether initial CR/PR and SD indicate similar survival benefits or not in advanced NSCLC patients receiving chemotherapy. This may be due to the complexity of SD that exhibits minor increases and decreases: When SD is achieved, some patients experience tumor shrinkage of <30% in the diameter of the target lesions, whilst others experience tumor increases of <20% in the diameter of the target lesions. These 'decreased' SD and 'increased' SD may have different behavior. In the present patients, there was no statistical significant difference in survival time between the patients with SD and those with CR/PR.

In clinical trials and in practice, prolongation of survival time appears to have been recorded in NSCLC patients in recent years, which may have been due to the appearance of more effective and less toxic drugs (17), molecular targeting agents (18-22) and the improvement of supportive therapy, such as G-CSF (23) and antiemetic drugs (24). In the present study, the survival of all consecutive NSCLC patients in daily

practice was evaluated, therefore, the study included 'unfit' patients, who are usually excluded from clinical trials. However, it was notable that the OS time in these patients was not shorter than that observed in recent clinical trials (25-30). In addition, in the present patients treated with platinum and pemetrexed, the OS time was as long as that observed in the PARAMOUNT trial (16.9 months) (31). In patients treated with bevacizumab and those with maintenance therapy with the drug, the OS time in the present study was evaluated to be as good as that of previous clinical trials (32-33). Our 'daily clinical practice' results provide information for the near future treatment of NSCLC patients. We believe that these favorable results are largely dependent on the power of novel antitumor drugs, such as pemetrexed, tyrosine kinase inhibitors and bevacizumab.

Despite these significant findings, the present study has certain limitations. The first limitation was inherent to the retrospective design of the study: lead time and length time biases could not be avoided. Second, OS time may have been affected by other factors, such as the effects of second-line and subsequent therapies. Third, the study period was so long that various regimens were enrolled. Not only novel antitumor drugs, but also improvements in supportive care and advances in imaging techniques may have conferred favorable effects for the survival of patients in recent years. Fourth, the RECIST criteria were not always applied to clinical chemotherapy decisions in daily practice. If SD is achieved in daily practice, careful consideration is required to decide whether or not to continue the chemotherapy using the same regimen.

Regardless of these limitations, the findings of the present study have certain clinical significance for the management of future NSCLC patients of unselected groups. The results confirmed that careful consideration is required in treating NSCLC patients who experience SD with chemotherapy.

In conclusion, if the primary outcome of chemotherapy for NSCLC at present is not shrinkage of the tumor, but is the prolongation of survival, chemotherapy would provide a clinical benefit not only for the 20% of patients with a good response who have CR/PR, but also for the 70% of disease-controlled patients who have SD, PR and CR.

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