Who Are Less Likely to Receive Subsequent Chemotherapy Beyond First-Line Therapy for Advanced Non-small Cell Lung Cancer?

Implications for Selection of Patients for Maintenance Therapy

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Background: Prospective studies have implied that maintenance therapy for non-small cell lung cancer (NSCLC) has its effect by giving active drugs earlier to patients who otherwise die without receiving second-line therapy. The purpose of this study was to select patients with NSCLC who could most benefit from maintenance therapy, by evaluating which patients would be less likely to receive second-line therapy.

Methods: Clinicopathologic data of patients with advanced NSCLC who received four cycles of first-line chemotherapy followed by time-off therapy and eventual disease progression or death were reviewed retrospectively. Patients were grouped into ones with first-line therapy only or ones with more than first-line therapy. Clinical characteristics between the two groups were compared.

Results: A total of 271 patients were eligible for analysis, and 39 patients (14.4%) received only first-line therapy. Patients significantly more likely to receive only first-line therapy had performance status of two or three after first-line therapy, large volume of initial target lesions (sum of long diameters $\geq$70 mm), or smaller decrease in target lesions (decrease $<$20%) after first-line therapy. Median overall survival of the 143 patients (52.8%) with at least one of these characteristics (16.3 months) was significantly shorter than that of patients without any of these characteristics (23.5 months, $p = 0.007$).

Conclusion: Maintenance therapy may be of greater benefit to patients with NSCLC who have clinical characteristics including poor performance status after first-line therapy, large initial target lesions, or smaller decrease in target lesions after first-line therapy.

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The current practice of first-line therapy for advanced non-small cell lung cancer (NSCLC) is four or six cycles of platinum-based combination chemotherapy followed by treatment break in nonprogressive status, which prolongs overall survival.[1] Despite modest progress in improving overall survival, the majority of patients experience disease progression and need further systemic treatment. One strategy to improve survival has been to use maintenance therapy in patients who derive benefit from first-line therapy.[2–5] Although the definition of maintenance therapy is controversial, it can be recognized as two designs. The first design is the continuation of the same drug used in initial therapy until a specified number of extended cycles or disease progression. The other design is switching to a different drug before disease progression after a defined number of cycles of first-line therapy.

In an era when many drugs approved for second-line therapy are available, the early switching to a noncross resistant second-line drug seems reasonable, and its efficacy has been demonstrated recently. In two recent trials, immediate switching to docetaxel or pemetrexed after four cycles of first-line therapy improved progression-free survival and overall survival significantly, when compared with delayed administration of second-line drugs at the time of disease progression.[6,7] However, one reason for lower survival with delayed therapy may be that many patients randomly assigned to the delayed arm never receive further systemic therapy: 37 and 33% of patients in the delayed arm did not receive second-line therapy in the studies with docetaxel and pemetrexed, respectively. Overall survival for patients who actually received docetaxel at the time of progression in the delayed arm was identical to that of patients with immediate docetaxel therapy.

These findings imply that the efficacy of maintenance therapy may be greater for patients who would have no chance to receive active second-line drugs if they had not

received it immediately after first-line therapy. Thus, the selection of patients less likely to receive second-line therapy later is important at the time of deciding whether to maintain or delay therapy after four or six cycles of platinum-based first-line therapy. Maintenance therapy for selected patients rather than all patients will decrease the cost and inconvenience of maintenance therapy without impairing its efficacy.

The aim of our study was to select patients who could most benefit from maintenance therapy, by identifying patients more likely to be unable to receive second-line therapy after being off therapy with nonprogressive disease after four cycles of first-line therapy for advanced NSCLC.

PATIENTS AND METHODS

We retrospectively screened consecutive patients who received first-line chemotherapy for advanced NSCLC at Samsung Medical Center between January 2003 and December 2008. The study population comprised patients who were off therapy with nonprogressive disease and did not receive maintenance therapy after four cycles of platinum-based first-line therapy. The decision to discontinue chemotherapy after four cycles of first-line therapy was made at the clinician's discretion after discussion with the patient. During the period of treatment break, the patients were followed up monthly and were evaluated by computed tomography scan every 3 months or when clinically indicated. Patients who experienced disease progression or death while off therapy were included in the analysis.

Clinicopathologic and follow-up data for these patients up to August 2009 were retrieved from medical records. Tumor burden was assessed by checking the number of organs involved with lung cancer and by calculating the sum of long diameters of target lesions based on the Response Evaluation Criteria in Solid Tumor, version 1.0. We blindly and independently evaluated change in target lesions by reviewing radiologically the computed tomographic images before and after two and four cycles of chemotherapy. This study was approved by the Institutional Review Board of Samsung Medical Center.

Statistical Analysis

Statistical analysis compared overall survival between patients who received first-line therapy only and patients who had more than first-line therapy by using the log-rank test. Overall survival encompassed the time from the first cycle of first-line therapy until the date of death or the last documented follow-up.

Clinical characteristics including sex, age, smoking status, performance status at the time of decision to discontinue chemotherapy, histology, stage, history of brain metastasis, the number of organs involved with lung cancer, regimen of first-line therapy, the sum of long diameters of all target lesions before and after first-line therapy, and the amount of decrease of target lesions during first-line therapy were evaluated as possible predictive indicators of the likelihood of receiving second-line therapy. The proportions of these characteristics between groups with first-line therapy only and with more than first-line therapy were compared using univariate analysis and multivariate logistic regression analysis. To evaluate more exactly the relationship between response to first-line therapy and the likelihood of receiving second-line therapy, we compared the proportion of patients whose target lesions decreased by $\geq$20 versus $<$20% in each group and $\geq$30% (partial response) versus $<$30% (stable disease). Tests were two sided, and $p < 0.05$ was considered statistically significant.

RESULTS

In total, 765 consecutive patients with advanced NSCLC received first-line chemotherapy, including 271 patients (35.4%) who were off therapy with nonprogressive disease after four cycles of first-line therapy but eventually experienced disease progression or death, who formed the study group for analysis. Patients excluded from analysis included 297 patients (38.8%) who experienced disease progression or were lost to follow-up during four cycles of first-line therapy, 145 patients (19.0%) who received more than four cycles of first-line therapy, and 52 patients (6.8%) who received maintenance therapy or had sustained nonprogressive disease after first-line therapy.

Table 1 shows clinical characteristics for the total sample and the subgroups who received first-line therapy only and who received more than first-line therapy. Median follow-up was 14.3 months (95% confidence interval [CI]: 13.0–15.6 months). Median age was 59 years (range, 23–77 years). Median interval from decision to discontinue first-line therapy to first follow-up was 28.0 days (95% CI: 26.9–29.1 days). Among 23 patients with performance status of two or three at the time of decision to discontinue first-line therapy, 19 patients (82.6%) had a good performance status (0 or 1) before first-line chemotherapy. Of the 271 patients in the study sample, 253 patients (93.4%) had at least one target lesion.

Among the 271 patients, 39 patients (14.4%) could not receive second-line therapy after four cycles of first-line chemotherapy because of disease progression and poor performance status ($n = 31$), death ($n = 4$), and patients' refusal ($n = 4$). For the 232 patients (85.6%) who received second-line therapy at the time of disease progression, the regimens were pemetrexed ($n = 71$), docetaxel ($n = 48$), gefitinib ($n = 46$), gemcitabine ($n = 32$), erlotinib ($n = 29$), and others ($n = 6$). Median interval from the date of decision to discontinue first-line therapy to the date of disease progression was significantly shorter in the group who received first-line therapy only (1.9 months) than in the group with more than first-line therapy (3.2 months, $p < 0.001$). In addition, median survival of patients who received first-line therapy only (6.7 months) was significantly shorter than that of patients who received more than first-line therapy (23.0 months, $p < 0.001$, Figure 1).

Clinical characteristics were compared between groups with first-line therapy only and with more than first-line therapy (Table 1). Significantly, more patients with poor performance status after chemotherapy, large volume of target lesions before and after first-line therapy, and with less decrease in target lesion size during first-line therapy could not receive second-line therapy in univariate analysis. Median interval from decision to discontinue first-line therapy to

TABLE 1. Comparison of Clinical Characteristics Between Groups with First-Line Therapy Only and with More Than First-Line Therapy

Characteristics	All Patients, *n* (%)	Patients with First-Line Therapy Only, *n* (%)	Patients with More Than First-Line Therapy, *n* (%)	*p*
All patients (%)	271 (100)	39 (100)	232 (100)	
Sex				
Male	189 (69.7)	32 (82.1)	157 (67.7)	0.07
Female	82 (30.3)	7 (17.9)	75 (32.3)	
Elderly				
Age ≥65 yr	84 (31.0)	16 (41.0)	68 (29.3)	0.14
Age <65 yr	187 (69.0)	23 (59.0)	164 (70.7)	
Performance status after first-line therapy				
0 or 1	248 (91.5)	30 (76.9)	218 (94.0)	<0.001
2 or 3	23 (8.5)	9 (23.1)	14 (6.0)	
Smoking				
Ever	167 (61.6)	29 (74.4)	138 (59.5)	0.08
Never	104 (38.4)	10 (25.6)	94 (40.5)	
Histology				
Adenocarcinoma	187 (69.0)	29 (74.4)	158 (68.1)	0.43
Nonadenocarcinoma	84 (31.0)	10 (25.6)	74 (31.9)	
Stage				
IIIB	56 (20.7)	6 (15.4)	50 (21.6)	0.38
IV	215 (79.3)	33 (84.6)	182 (78.4)	
Brain metastasis before therapy				
Yes	40 (14.8)	8 (20.5)	32 (13.8)	0.27
No	231 (85.2)	31 (79.5)	200 (86.2)	
Number of involved organs				
≥3	38 (14.0)	5 (12.8)	33 (14.2)	0.82
<3	233 (86.0)	34 (87.2)	199 (85.8)	
Regimen of first-line therapy				
Gemcitabine plus platinum	202 (74.5)	29 (74.4)	173 (74.6)	0.97
Paclitaxel plus platinum	16 (5.9)	2 (5.1)	14 (6.0)	
Docetaxel plus platinum	52 (19.2)	8 (20.5)	44 (19.0)	
Etoposide plus platinum	1 (0.4)	0 (0)	1 (0.4)	
Sum of long axes of target lesions before therapy	253 (100)	37 (100)	216 (100)	0.03
≥70 mm	49 (19.4)	12 (32.4)	37 (17.1)	
<70 mm	204 (80.6)	25 (67.6)	179 (82.9)	
Sum of long axes of target lesions after therapy	253 (100)	37 (100)	216 (100)	0.036
≥50 mm	50 (19.8)	12 (32.4)	38 (17.6)	
<50 mm	203 (80.2)	25 (67.6)	178 (82.4)	
Decrease in target lesion	253 (100)	37 (100)	216 (100)	0.12
<30%[a]	141 (55.7)	25 (67.6)	116 (53.7)	
≥30%[a]	112 (44.3)	12 (32.4)	100 (46.3)	
Decrease in target lesion	253 (100)	37 (100)	216 (100)	0.015
<20%	98 (38.7)	21 (56.8)	77 (35.6)	
≥20%	155 (61.3)	16 (43.2)	139 (64.4)	

[a] The amount of the change represented stable disease (decrease <30%) and partial response (decrease ≥30%) by response evaluation criteria in solid tumor.

first follow-up was not different between the two groups (28 days versus 30 days, $p = 0.38$).

In multivariate analysis, clinical characteristics including poor performance status, large volume of target lesions before therapy, and less decrease of target lesions during first-line therapy were significantly associated with a greater likelihood of receiving only first-line therapy (Table 2). Among the study population, 143 patients (52.8%) had at least one of these clinical characteristics, and their median overall survival was significantly shorter (16.3 months) than

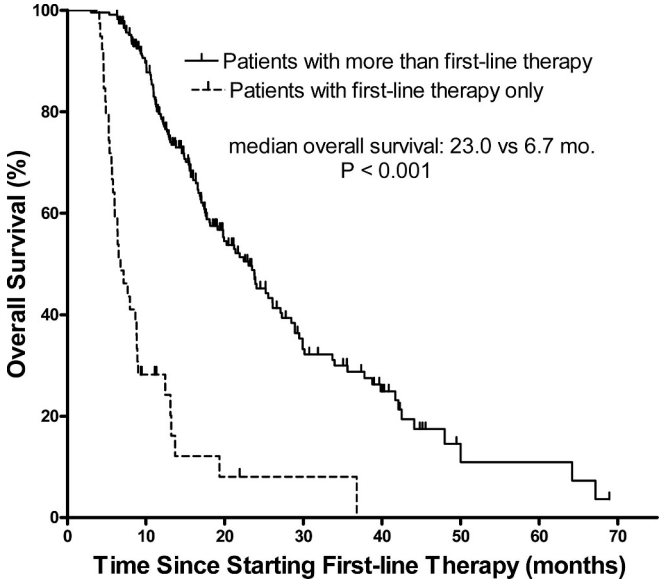

FIGURE 1. Overall survival curves of patients who received first-line therapy only and patients who received more than first-line therapy.

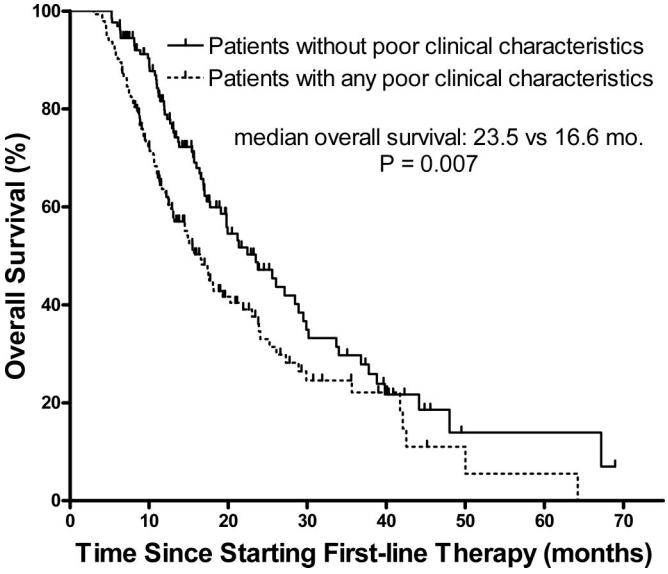

FIGURE 2. Overall survival curves of patients with and without the clinical characteristics including poor performance status at the time of decision to discontinue first-line therapy, large target lesions before first-line therapy, or less decrease in target lesions after first-line therapy.

TABLE 2. Multivariate Analysis of Clinical Characteristics Associated with Receiving Only First-Line Therapy

Characteristics	Odds Ratio	95% CI
Poor performance status after first-line therapy: 2 or 3 (vs. 0 or 1)	4.83	1.75–13.36
Less decrease in target lesions after first-line therapy: <20% (vs. ≥20%)	2.47	1.12–5.44
Great sum of long axes of target lesions before first-line: therapy ≥70 mm (vs. <70 mm)	3.83	1.02–14.36
Great sum of long axes of target lesions after first-line therapy: ≥50 mm (vs. <50 mm)	0.72	0.20–2.61

CI, confidence interval.

that of patients without any of these characteristics (23.5 months, $p = 0.007$, Figure 2).

DISCUSSION

The optimal therapeutic approach for advanced NSCLC has been increasingly difficult to define. First-line therapy for advanced NSCLC is commonly done with four cycles (in some cases with six cycles) of platinum-based doublets.[8] However, there is no consensus regarding the appropriate treatment strategy for patients who are in nonprogressive status after the completion of platinum-based first-line therapy. Many patients have a treatment break, and second-line therapy is administered at the time of disease progression. The value of delayed administration of second-line therapy was recently supported by the observation of Fidias et al.[7] that overall survival for patients on the delayed docetaxel arm who actually received docetaxel was identical with that of patients on immediate docetaxel arm. However, many patients never receive second-line therapy due to rapid disease progression combined with deteriorating performance status after a certain period of treatment break, and they die earlier. Maintenance therapy is used to address this shortcoming of current practice.

The extended administration of effective first-line therapy has been tried in many studies.[9–14] First-line chemotherapy was administered until a defined number of extended cycles or disease progression. In a previously reported study,[14] we randomly assigned patients without progression after two cycles of a platinum doublet to either two or four more chemotherapy cycles of the same. There was no difference in the primary end point, 1-year survival, despite of time to progression favoring the more chemotherapy arm (6.2 versus 4.6 months, $p = 0.001$). More patients who received less first-line therapy were able to eventually receive more second-line therapy (74.4 versus 62.7%, $p = 0.026$), perhaps accounting for the lack of difference in overall survival between the two arms. Many studies also failed to demonstrate improved survival with extended first-line therapy. In addition, toxicity was greater, and quality of life was worse with prolonged initial therapy in meta-analysis. Thus, the prevailing opinion was that a brief duration of initial first-line therapy is best. However, a recently published phase II study showed that pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous NSCLC provided progression-free survival of 7.8 months and overall survival of 14.1 months.[15] In view of the modest toxicity of pemetrexed, maintenance pemetrexed therapy after initial therapy with pemetrexed plus platinum could be a promising treatment sequence, and we anticipate the results of an ongoing phase III trial.[16]

On the other hand, maintenance therapy with an alternative effective drug after initial chemotherapy has already validated its role by showing significantly increased overall survival. In the clinical trial in advanced NSCLC reported by Ciuleanu et al.,[6] patients received platinum-based doublet regimen as first-line therapy. Those without progression after four cycles of chemotherapy were randomly assigned to pemetrexed or placebo. Median overall survival was 10.6 months in the placebo group compared with 13.4 months in the pemetrexed group (95% CI: 0.65–0.91). In another study, sequential erlotinib immediately after four cycles of platinum-based doublet extended overall survival compared with the control arm (95% CI: 0.70–0.95).[17] However, a considerable number of patients in the control arm could not receive effective second-line drugs when disease progression was detected.[6,7,17] These findings suggest that improved survival with maintenance therapy can be attributed to the fact that more patients are able to receive more active drugs. Thus, maintenance therapy may achieve its effect because active drugs administered before disease progression can prevent complications of the disease from rendering patients unable to receive it. On the basis of this reasoning and the fact that the cost and inconvenience of maintenance therapy is substantial, we tried to select patients who could most benefit from maintenance therapy after four cycles of first-line therapy.

This retrospective analysis showed that patients with poor performance status at the time of decision to discontinue first-line therapy, large volume of target lesions before first-line therapy, or less decrease in target lesions after first-line therapy were more likely to receive only first-line therapy (i.e., to be unable to receive second-line therapy). Thus, we suggest that earlier or immediate administration of effective drugs should be considered to these patients after first-line therapy.

Significantly, more patients with poor performance status at the time of discontinuing first-line chemotherapy did not receive second-line therapy. Change in performance status during first-line therapy may be associated with disease progression or treatment. Most patients with poor performance status after first-line therapy had good performance status before platinum-based first-line chemotherapy. This finding suggests that deteriorating performance status could be caused in part by platinum-based chemotherapy, because there was no definite disease progression during their first-line therapy. Newly proven second-line drugs, such as pemetrexed or erlotinib, have less toxicity than other chemotherapeutic agents.[18,19] Maintenance therapy with more tolerable second-line drugs for patients with deteriorating performance status after initial platinum-based chemotherapy may be a useful strategy to improve survival without further undermining performance status.

Tumor burden assessed by the number of cancer-involved organs was not associated with the probability of receiving second-line therapy. We also evaluated whether the metastatic site would impact the probability of receiving second-line therapy. There was a trend for patients with brain metastasis to be less likely to receive second-line therapy but without statistical significance ($p = 0.27$). Other metastatic sites, such as liver and bone, also did not impact on whether patients received second-line therapy.

Another strategy to improve treatment outcome might be the early detection of disease progression using careful follow-up after the completion of first-line therapy. The interval of follow-up should be individualized depending on the clinical presentation and pace of disease progression. Our results showed that disease progressed more rapidly in patients who could not receive second-line therapy after discontinuing first-line therapy. Based on our results, patients with characteristics including poor performance status, large volume of initial target lesions, and less decrease in target lesions should be followed up more closely if they do not receive maintenance therapy.

Our study had some limitations. It was retrospective in nature, and the study population was too small to conclude which patients should or should not receive maintenance therapy. Furthermore, this study is based on a basic premise but unvalidated that maintenance therapy may be most beneficial for patients who would have no chance to receive active second-line drugs if they had not received it immediately after first-line therapy. Therefore, it is too premature to be applied directly to the clinical practice, and we need additional studies for confirmation. In addition, the proportion of patients who did not receive second-line therapy (14.4%) was much lower than that of prospective studies (37 or 33%). This phenomenon can be explained by the relatively frequent follow-up after completion of first-line therapy in our patient population. Despite these limitations, to our knowledge, this study is the first attempt to select patients for maintenance therapy in NSCLC.

In summary, maintenance therapy before disease progression would benefit some patients with NSCLC in terms of survival. However, the important goal of cancer treatment is decreasing treatment-associated toxicity and extending survival. Therefore, maintenance therapy should be reserved for selected patients who will most benefit from it. Clinical characteristics including poor performance status after first-line therapy, large volume of target lesions before first-line therapy, and less decrease in target lesions after first-line therapy were associated with a lower likelihood of receiving subsequent lines of therapy beyond first-line therapy, and patients with these characteristics may benefit the most from maintenance therapy.

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