A Landmark Point Analysis with Cytotoxic Agents for Advanced NSCLC

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Introduction: As a result of recent publications, we hypothesized that period of 8 weeks after initiation of treatment is a useful landmark point for cytotoxic agents for advanced non-small cell lung cancer (NSCLC). To test this hypothesis, we conducted landmark analyses with clinical trials employing cytotoxic agents. Our goal was to assess the proper design of clinical trials with cytotoxic agents for NSCLC for maximizing patients' benefit.

Methods: We conducted landmark analyses of a phase II study of pemetrexed in locally advanced or metastatic NSCLC and a phase III study of Four-Arm Cooperative Study for advanced NSCLC. A total of 806 patients who received chemotherapy (pemetrexed, cisplatin and irinotecan, paclitaxel and carboplatin, cisplatin and gemcitabine, cisplatin and vinorelbine) were included in this assessment.

Results: Tumor-shrinkage rate at 8 weeks was significantly associated with longer survival in the study with pemetrexed ($p = 0.043$), whereas tumor-shrinkage rate at 4 weeks did not correlated with survival ($p = 0.139$). Similarly, using the Four-Arm Cooperative Study data, the optimal landmark point was 8 weeks ($p = 0.002$), not 4 weeks ($p = 0.190$).

Conclusion: The landmark point for NSCLC was 8 weeks with all cytotoxic agents in our analysis when the therapy was given as a frontline or subsequent therapy. Our result suggests the concept of a disease-specific landmark point, which may lead to a change of phase II/III clinical study design to evaluate cytotoxic agents and clinical investigators, and their sponsors may consider an early look to assess the efficacy of cytotoxic agents for NSCLC.

Key Words: NSCLC, Landmark analysis, Pemetrexed, Clinical trial.

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Non-small cell lung cancer (NSCLC) is the most common type of lung cancer worldwide and many clinical studies are currently assessing new chemotherapy combinations for NSCLC.[1–5] Currently, in most phase II/III, clinical trials for advanced NSCLC use overall survival (OS) as a primary end point[6–10] and patients continue treatment until progressive disease (PD), unacceptable toxicity, or withdrawal of consent,[11–13] resulting in the median number of cycles being delivered from three to four. Treatment is discontinued for disease refractory to treatment or the patient could not tolerate the toxicities of treatment beyond three to four cycles.[13] Also, it was reported that objective responses and palliation of symptoms typically occurred within the first two to three cycles of therapy.[14]

Therefore, we attempted to assess the proper design of clinical trial targeting advanced NSCLC, including duration of treatment and optimal response measurement.

To assess the proper length of clinical study for NSCLC, we conducted landmark analyses of NSCLC clinical trials. The landmark method is a valid method for evaluating survival by tumor response.[15] Recently, landmark survival analysis of a large Southwest Oncology Group database revealed that week 8 is a landmark point for first-line therapy for advanced NSCLC with platinum-based chemotherapy.[16]

In this study, we also hypothesized that week 8 is a landmark point for advanced NSCLC patients with any cytotoxic regimens regardless of line of therapy. To test this hypothesis, we conducted landmark survival analyses of a phase II study of pemetrexed as salvage in metastatic NSCLC patients who have prior chemotherapy (the pemetrexed phase II study),[17] and Four-Arm Cooperative Study (the FACS study) a phase III study for previously untreated advanced NSCLC.[18] The present study will potentially provide scientific evidence supporting change of the paradigm for late phase clinical trial design.

PATIENTS AND METHODS

Original Clinical Studies

These landmark analyses were performed on two clinical studies. One was a phase II study of pemetrexed as salvage in metastatic NSCLC patients who had prior chemotherapy.[17] In this phase II study, pemetrexed 500 or 1000 mg/m^2 was administrated every 3 weeks. Patients had to meet the following inclusion criteria: clinical stage III or IV NSCLC, at least one target lesion, one or two prior chemotherapeutic regimens, age 20 to 75 years old, Eastern Cooperative Oncology Group performance status 0 to 2, and adequate hematological, hepatic, and renal functions.

The other was a phase III cooperative group study of four arms for advanced untreated NSCLC patients.[18] In the four arms of this phase III study, the combination chemotherapies of cisplatin plus irinotecan, paclitaxel plus carbopla-

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tin, cisplatin plus gemcitabine, or cisplatin plus vinorelbine were given, respectively: cisplatin 80 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, 15 every 4 weeks (IP); carboplatin area under the curve 6.0 minutes × mg/ml on day 1 plus paclitaxel 200 mg/m^2 on day 1 every 3 weeks (TC); cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1, 8 every 3 weeks (NP). Patients had to meet the following criteria: clinical stage IIIB or IV NSCLC, no prior chemotherapy, no prior surgery and/or radiotherapy for the primary site, age 20 to 74 years old, Eastern Cooperative Oncology Group performance status 0 or 1, and adequate hematological, hepatic, and renal functions.

In all five treatment arms of these two studies, tumor sizes were assessed every 4 weeks by diagnostic computed tomography scan (slice thickness ≤10 mm) and the evaluation of tumor response was performed using the RECIST criteria.

Original publications have already been published;[17,18] however, the result reported in this article is not shown in both previous publications.

Statistical Analysis

Statistical analyses were carried out to assess the association of the intermediate outcomes with OS, using the landmark method which could evaluate responses for all patients at some fixed time after the onset of treatment.[19] Briefly, using data of the pemetrexed phase II study or the FACS study, two separate analyses were completed at 4 and 8 weeks from the start of treatment. In each analysis, patients are divided into two groups according to their tumor-shrinkage rates (TSRs). "TSR ≥0%" means tumor size "decreased" or "no change." All patients who were eligible for efficacy analysis were categorized as responder (TSR ≥0) or nonresponder (TSR <0) at the landmark point. A logrank test was used to assess the association between disease status at the landmark times. The data analysis was generated using SAS/STAT software, Version 8.2 of the SAS system for PC (SAS Inc., Cary, NC).

RESULTS

Patient Characteristics

The Pemetrexed Phase II Study

Table 1 summarizes the characteristics of patients included in the pemetrexed registration study. Two hundred twenty-six patients were enrolled into this study and received pemetrexed 500 mg/m^2 or 1000 mg/m^2 every 3 weeks. At the time of unblinding and study analysis, 10 patients had discontinued therapy. Therefore, 216 patients were evaluable for efficacy: 137 male (63%) and 79 female (37%). One hundred seventy three patients (80%) had stage IV disease and 43 patients (20%) had stage IIIB disease. A total of 72.7% patients were diagnosed as adenocarcinomic. Prior to pemetrexed all patients received one or two chemotherapy regimens.

The FACS Study

The characteristics of patients included in the FACS study are shown in Table 1. A total of 602 patients were randomly assigned into one of four regimens: cisplatin 80 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, 15 every 4 weeks (IP); carboplatin area under the curve 6.0 minutes × mg/ml on day 1 plus paclitaxel 200 mg/m^2 on day 1 every 3 weeks (TC); cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1, 8 every 3 weeks (NP). Ten patients did not receive chemotherapy and 11 patients were subsequently found to be ineligible. Therefore, 581 patients were assessable for efficacy: 398 male (69%) and 183 female (31%). Four hundred sixty-six patients (80%) had stage IV disease and 115 patients (20%) had stage IIIB disease.

Best Response to Treatment and Survival

Table 2 and Figures 1*A*, *B* show best response to treatment and OS in the pemetrexed phase II study and the FACS study.

TABLE 2. Best Response to Treatment in a Phase II Study of Pemetrexed and FACS Study

Clinical Study	Phase II Study of Pemetrexed	FACS Study
No. of patients	216	581
Response		
CR	0	1 (0.2%)
PR	36 (16.7%)	183 (31.5%)
SD	74 (34.3%)	245 (42.2%)
PD	106 (49.1%)	120 (20.7%)
Not evaluated	0	32 (5.5%)

FACS, Four-Arm Cooperative Study; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

TABLE 1. Patients Characteristics and Treatment Delivery in Phase II Study of Pemetrexed and FACS Study

Chemotherapy	Pts	Gender (Male/Female)	Age Median (Range)	PS (PS0/PS1/PS2)	Histology			Stage IIIB/IV
					Adeno	Squamous	Others	
Pemetrexed[17]	216	137/79	62 (26–74)	79/125/12	157	48	11	43/173
Cisplatin/irinotecan[18]	145	97/48	62 (30–74)	44/101/0	121	16	8	31/114
Carboplatin/paclitaxel[18]	145	99/46	63 (33–74)	44/101/0	104	31	10	28/117
Cisplatin/gemcitabine[18]	146	101/45	61 (34–74)	45/101/0	108	29	9	30/116
Cisplatin/vinorelbine[18]	145	101/44	61 (28–74)	45/100/0	109	29	7	26/119

Pts, number of patients; PS, performance status; FACS, Four-Arm Cooperative Study.

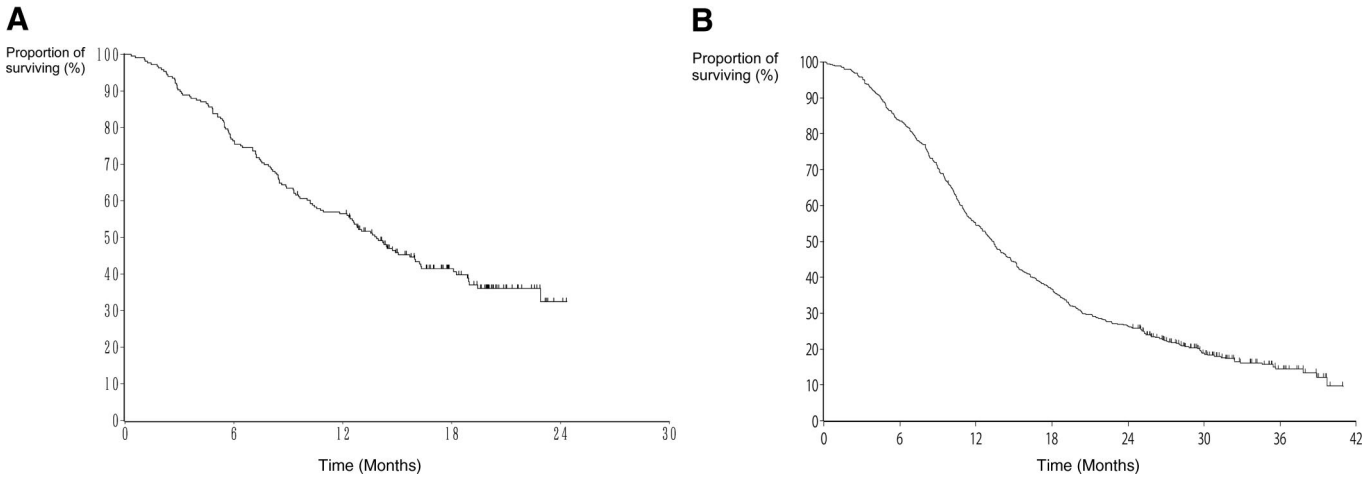

FIGURE 1. Overall survival curve by Kaplan-Meier. Phase II study of Pemetrexed (*A*) and Four-Arm Cooperative Study (FACS) (*B*).

TABLE 3. Tumor Shrinkage Rate in the Phase II Pemetrexed Study and in the FACS Study

	4 wk		8 wk	
Items	**Decrease or No Change**	**Increase**	**Decrease or No Change**	**Increase**
Phase II study of Pemetrexed				
No. of patients	91	56	119	76
No. of events	54	38	62	50
MST (mo)	13.0	10.5	14.5	10.4
95% CI	11.3–18.0	6.5–13.5	10.8–NA*	6.6–13.0
Log-rank test	$p = 0.139$		$p = 0.043$	
FACS Study				
No. of patients	328	43	497	61
No. of events	264	37	403	55
MST (mo)	12.6	12.2	12.1	8.8
95% CI	11.4–14.3	9.1–13.4	11.0–13.5	7.2–12.0
Log-rank test	$p = 0.190$		$p = 0.002$	

* Not calculated because of censored events.

FACS, Four-Arm Cooperative Study; MST, median survival time; CI, confidence interval.

Landmark Point

As shown in Table 3 and Figure 2*A*, using data of the pemetrexed phase II study, there was a survival advantage among patients who had achieved a response (TSR $\geq$0) at 8 weeks after registration ($p = 0.043$), whereas there was no significant association between response and survival at 4 weeks after registration ($p = 0.139$). Table 3 and Figure 2*B* demonstrate that 8 weeks is also a landmark point with patients participated in the FACS study ($p = 0.002$), whereas there was no survival advantage among patients who achieved a response (TSR $\geq$0) at 4 weeks after registration ($p = 0.190$).

DISCUSSION

Duration of Treatment

In 1989, Buccheri et al.[20] reported a randomized trial of nonplatinum-based chemotherapy with stable disease (SD) after two or three cycles of chemotherapy to continued treatment or best supportive care. No survival benefit was seen with continuous treatment in this subset of patients with SD. In 2001, Smith et al.[21] reported a randomized trial of three cycles versus six cycles of platinum-based chemotherapy in 308 patients with stage III/IV advanced NSCLC. Of the patients randomized to three cycles, 72% completed therapy, whereas only 31% of the patients randomized to six cycles completed therapy.[21] No advantage was seen for the longer duration of therapy.[21] In addition, more toxicity was reported compared with patients receiving the longer duration (six cycles) of therapy. In 2007, Park et al.[22] demonstrate improved time to progression with extended duration of platinum-based therapy (four cycles versus six cycles), without no survival benefit. In 2008, Lara et al.[16] reported that week 8 is a landmark point for first-line therapy for advanced NSCLC with platinum-based chemotherapy. Although Lara et al. used disease control rate (DCR), instead of using traditional response rate, it was shown that tumor response at week 8 was significantly associated with survival benefit for advanced NSCLC patients treated with platinum-based chemotherapy.

In this study, we conducted landmark analyses with the pemetrexed phase II and the FACS studies. In line with the previous report of Lara et al., our data demonstrate that week 8 is a landmark point for FACS study, which is four-armed comparison study of platinum-based regimens (cisplatin plus irinotecan, paclitaxel plus carboplatin, cisplatin plus gemcitabine, and cisplatin plus vinorelbine) as a frontline-combination therapy. Interestingly, tumor response at week 8 is also correlated to survival benefit in patients treated with pemetrexed as a salvage agent, which supports previous studies reporting that objective responses and palliation of symptoms typically occurred within the first two to three cycles of therapy.[14]

For landmark analysis, all available patients' data were used. However, tumor response was not assessed precisely every 4 weeks and some patients did not get response assessment at week 4. Thus, there are potential limitations for determination of an accurate landmark point and we can not

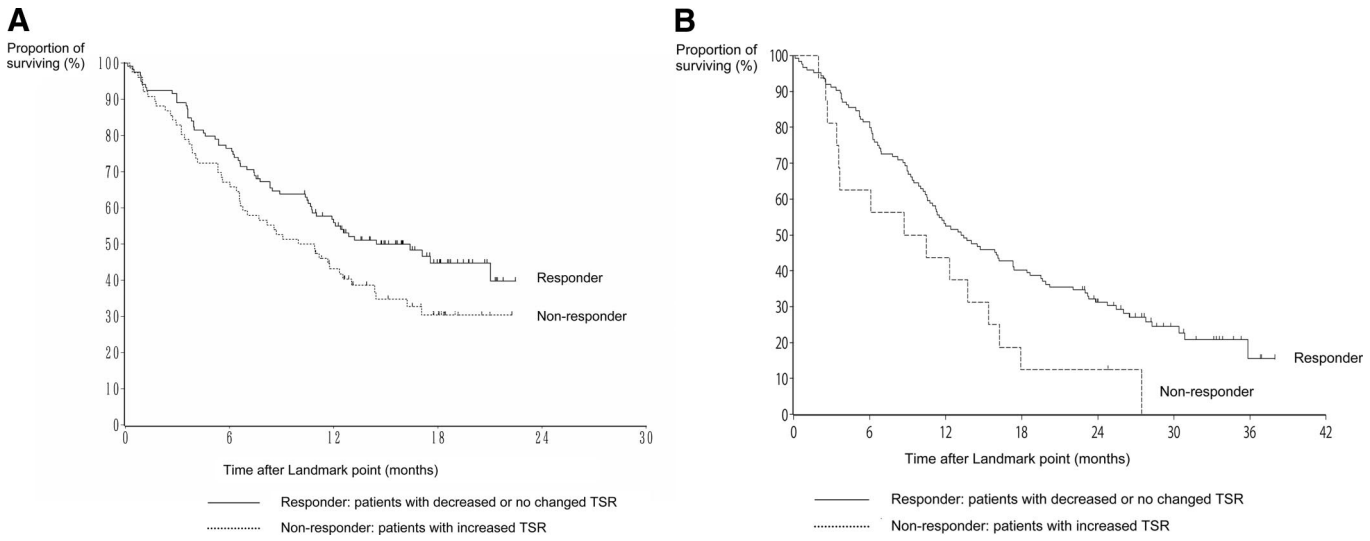

FIGURE 2. Survival by response at week 8. Phase II study of Pemetrexed (*A*) and Four-Arm Cooperative Study (FACS) (*B*).

deny the possibility for week 4 as a landmark point. To get more accurate landmark point, future confirmation with additional week 4 data were required. Furthermore, to achieve equivalent precision to previous report by Lara et al.,[16] the landmark point at week 8, actually means between week 4 and week 12.

Tumor Response Assessment

For tumor response assessment, Lara et al. used DCR consisting of complete response (CR), partial response (PR), and SD instead of the traditional response rate of CR + PR.[16] In 1999, Sekine et al.[23] reported that PD rate has a better correlation with median survival time than traditional response rate by reviewing 42 single agent phase II studies for advanced NSCLC (3063 patients). Both previous reports suggested that SD might be clinically relevant. According to RECIST criteria, PR is defined as 30% or greater decrease in the sum of the measurable lesions and PD as a 20% or greater increase or appearance of new lesions.[24] Therefore, achievement of SD does not necessarily mean "nonresponders," and there are both "responders" and "nonresponders" in SD patients. In another word, with defining the responding patients as "having any shrinkage (TSR $\geq$0%)" versus "no shrinkage (TSR $<$0%)" at the landmark point, SD patients were divided into two groups: "SD with good prognosis" versus "SD with poor prognosis."

To differentiate responder from nonresponder, actual measure of tumor diameter is often used for landmark analysis assessing efficacy-related issue.[25,26] We demonstrated that TSR at week 8 was significantly associated with longer survival in both the pemetrexed phase II study and the FACS study. Our study not only confirmed previous reports[14,16] but also showed usefulness of TSR.

Application of Landmark Point

Together with the publication by Lara et al., week 8 may be a landmark point for advanced NSCLC patients with any cytotoxic treatments, regardless of the type of therapy. Our findings lend support to the idea that there might be a disease-specific landmark point, which has broad implications for future clinical trial design.

Although our results are preliminary and need to be validated in the prospective settings, proper length for clinical trials for advanced NSCLC can be much shorter. Clinical investigators and their sponsors may consider an early look to assess the efficacy of cytotoxic drugs for NSCLC. If this landmark point can be prospectively confirmed then TSR and/or DCR at week 8 can be used in phase II trials to screen new treatments for activity in advanced NSCLC instead of traditional endpoints such as response rate or progression-free survival.

As far as clinical trials are concerned, we can not deny that response is a marker which selects the good prognosis patient and nonresponder may be resistant to any treatments. To demonstrate superior efficacy in a comparison setting, switching experiments are required to provide evidence for a meaningful clinical benefit with changing therapy. However, the crossover design to evaluate anticancer drug has been considered difficult because of relatively short lung cancer patients' life in oncology in general. Our findings may help to optimize the balance between patients' survival benefit and scientific validity by providing statistical rationale for the switching point in crossover studies in cancer patients. Assessing the effectiveness of the switched therapy, we need to have appropriate efficacy parameters to evaluate potential of the agent used in a salvage setting, because it was previously reported that the agent is less effective and more toxic when it is used as a second-line treatment for NSCLC.[27–29] Our statistical rationale can still be useful to determine the duration of salvage therapy, and tumor response can be assessed at the landmark point from the point of change.

For clinical practice, our findings may provide a rationale for the overall management strategy of advanced NSCLC. If week 8 is validated for disease-specific landmark point of NSCLC with cytotoxic agents, the duration of first-line therapy

and timing of maintenance or sequential therapy should also be addressed prospectively using the landmark point.

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