original article

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The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer

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Background: Using data from a large phase III study of previously treated advanced non-small-cell lung cancer (NSCLC) that showed similar efficacy for pemetrexed and docetaxel, this retrospective analysis evaluates the impact of first-line chemotherapy on the outcome of second-line chemotherapy.

Patients and methods: In all, 571 patients with advanced NSCLC were randomly assigned to receive pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 on day 1 of a 21-day cycle. Comparisons were made based on type of first-line therapy [gemcitabine + platinum (GP), taxane + platinum (TP), or other therapies (OT)], response to initial therapy, time since initial therapy, and clinical characteristics. The two second-line treatment groups were pooled for this analysis due to similar efficacy and were assumed to have no interaction with the first-line therapies.

Results: Baseline characteristics were generally balanced. By multivariate analysis, gender, stage at diagnosis, performance status (PS), and best response to first-line therapy significantly influenced overall survival (OS). Additional factors by univariate analysis, histology, and time elapsed from first- to second-line therapy significantly influenced OS.

Conclusions: Future trials in the second-line setting should stratify patients by gender, stage at diagnosis, PS, and best response to first-line therapy.

Key words: chemotherapy, docetaxel, non-small-cell lung cancer, pemetrexed, survival

introduction

Current American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend treatment of advanced non-small-cell lung cancer (NSCLC) with platinum-based doublet combination chemotherapy in the first-line setting and with nonplatinum-based doublets as a reasonable alternative [1, 2]. These recommendations are based on multiple randomized clinical trials comparing various platinum-based doublets and nonplatinum-based doublets including trials of the Southwest Oncology Group and Eastern Cooperative Oncology Group (ECOG) [3–9].

Preliminary results of a randomized phase II/III trial, ECOG 4599 were reported at ASCO 2005, evaluating the role of bevacizumab (B) in addition to carboplatin and paclitaxel (PC) in selected NSCLC patients. The addition of B to PC is significantly superior in response (27% versus 10%, $P < 0.0001$), progression-free survival (6.4 months versus 4.5 months, $P < 0.0001$), and median survival (12.5 months versus 10.2 months, $P = 0.0075$) compared with the PC arm alone [10].

ASCO and NCCN guidelines recommend docetaxel, pemetrexed, or erlotinib in the second-line setting. These recommendations were based on randomized clinical trials comparing these agents with best supportive care or placebo plus best supportive care, respectively, in two randomized trials. Shepherd et al. [11] compared docetaxel 75–100 mg/m^2 with best supportive care in an international study of 204 patients. Median survival was 7.5 months versus 4.6 months that translated into a superior 1-year survival rate of 37% versus 12%, $P = 0.003$, favoring docetaxel 75 mg/m^2 over the control arm. In another study of 373 patients, Fossella et al. [12] compared docetaxel 75 or 100 mg/m^2 with the control group of either vinorelbine or ifosfamide. Subjects treated with docetaxel had significantly longer time to progression (TTP) versus the control group ($P = 0.046$). One-year survival was 32% for docetaxel 75 mg/m^2 versus 19% for vinorelbine or ifosfamide ($P = 0.025$); however, the overall survival (OS) time was not significantly different.

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A large randomized phase III comparison trial of pemetrexed to docetaxel showed similar survival with median survival times (MSTs) of 8.3 and 7.9 months, respectively [hazard ratio (HR), 0.99; 95% confidence interval (CI), 0.82 to 1.2] [13]. Objective and subjective response rates and TTP were also similar in the two arms. There were, however, significantly more grade 3/4 hematologic toxicity, febrile neutropenia, and drug-related hospitalizations on the docetaxel arm. On the basis of this trial and other trial data supporting pemetrexed results, the Food and Drug Administration (FDA) approved the use of pemetrexed in the second-line setting.

The BR.21 trial [14] was a large phase III trial of 731 patients who underwent 2 : 1 randomization to 150 mg oral erlotinib daily or placebo after failing one or two prior chemotherapy regimens. The erlotinib arm had a response rate of 8.9% versus <1% on the placebo arm ($P < 0.001$), and an OS rate of 6.7 months versus 4.7 months, respectively (HR 0.70; $P < 0.001$). On the basis of these data, docetaxel and pemetrexed are FDA-approved in the second-line setting, and erlotinib is approved in the second- or third-line setting.

On the basis of the aforementioned data, docetaxel and pemetrexed have received regulatory approval worldwide in the second-line setting, and erlotinib is approved for both the second- and third-line setting. With at least three agents approved for advanced NSCLC patients in the second-line setting and the development of new agents, it is probable that many randomized phase III trials will be comparing agents in the second-line setting. Optimal study design will require appropriate stratification on the basis of established prognostic factors. Factors that were prospectively stratified for in the randomized trial comparing pemetrexed with docetaxel in the second-line setting included the following: performance status (PS) at start of second-line therapy, prior platinum or paclitaxel use, number of prior chemotherapy regimens, time since last chemotherapy, best response to last chemotherapy, stage at diagnosis, baseline plasma homocysteine level, and center. In this retrospective analysis of the randomized trial, we evaluate age, gender, stage, PS at start of second-line therapy, type of first-line chemotherapy, response to first-line chemotherapy, and time elapsed from first- to second-line chemotherapy on survival outcome in the second-line setting [13]. Baseline values for lactate dehydrogenase, percent change in weight loss (<10%), and smoking history were not available.

patients and methods

The major efficacy and toxicity findings from the phase III trial comparing pemetrexed (Alimta, Eli Lilly and Company, Indianapolis, IN, USA) with

Table 1. Patient and disease characteristics for three groups (GP, TP, and OT)

	Total ($n = 571$)	GP ($n = 182$)	TP ($n = 113$)	OT ($n = 276$)	
Median age (range)	58 (22–87)	57 (22–79)	58 (40–87)	59 (30–81)	$P = 0.177$[a]
Gender					$P < 0.001$[b]
Female (%)	160 (28%)	53 (29%)	46 (41%)	61 (22%)	
Male (%)	411 (72%)	129 (71%)	67 (59%)	215 (78%)	
Stage III (%)	144 (25%)	33 (18%)	26 (23%)	85 (31%)	$P = 0.008$[b]
Stage IV (%)	427 (75%)	149 (82%)	87 (77%)	191 (69%)	
Histology					$P = 0.047$[b]
Adeno (%)	296 (52%)	97 (53%)	71 (63%)	128 (46%)	
Squamous (%)	171 (30%)	56 (31%)	25 (22%)	90 (33%)	
Other (%)	104 (18%)	29 (16%)	17 (15%)	58 (21%)	
Performance status	($n = 538$)	($n = 174$)	($n = 106$)	($n = 258$)	$P = 0.849$[b]
ECOG PS 0 (%)	100 (19%)	35 (20%)	19 (18%)	46 (18%)	
ECOG PS 1 (%)	374 (70%)	122 (70%)	74 (70%)	178 (69%)	
ECOG PS 2 (%)	64 (12%)	17 (10%)	13 (12%)	34 (13%)	
Best response to first-line therapy	($n = 545$)	($n = 179$)	($n = 113$)	($n = 253$)	$P = 0.714$[a]
CR	16 (3%)	7 (4%)	1 (1%)	8 (3%)	
PR	190 (35%)	66 (37%)	38 (34%)	86 (34%)	
SD	199 (37%)	63 (35%)	46 (41%)	90 (36%)	
PD	140 (26%)	43 (24%)	28 (25%)	69 (27%)	
Time elapsed to second-line therapy	($n = 563$)	($n = 179$)	($n = 113$)	($n = 271$)	$P = 0.003$[a]
≤3 months	277 (49%)	87 (49%)	61 (54%)	129 (48%)	
3–6 months	117 (21%)	50 (28%)	24 (21%)	43 (16%)	
≥6 months	169 (30%)	42 (23%)	28 (25%)	99 (37%)	
Number of metastatic sites	($n = 479$)	($n = 146$)	($n = 90$)	($n = 243$)	$P = 0.422$[b]
1	75 (16%)	22 (15%)	9 (10%)	44 (18%)	
2–3	251 (52%)	74 (51%)	50 (56%)	127 (52%)	
>4	154 (32%)	50 (34%)	31 (34%)	73 (30%)	

[a]P = analysis of variance.

[b]P = chi-square analysis.

GP, gemcitabine + platinum; TP, taxane + platinum; OT, other therapies; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; SD, stable disease; and PD, progressive disease.

Table 2. Survival univariate and multivariate analyses

Characteristics	Median survival	Univariate *P* value	Multivariate *P* value
Age			
<70	7.9	0.809	NA
≥70	8.8		
Gender			
Male	7.2	0.001	0.03
Female	9.4		
Stage			
III	9.5	0.036	0.012
IV	7.8		
Histology			
Adenocarcinoma	9.1	0.004	0.054
Squamous cell carcinoma	6.5		
Other/mixed	7.8		
Performance status			
0	12.7	<0.001	<0.001
1	8.3		
2	2.6		
Best response to first-line therapy			
CR/PR	15.8	<0.001	<0.001
SD	10.5		
PD	4.6		
Time elapsed to second-line therapy			
≤3 months	6.9	0.001	0.183
3–6 months	9.2		
≥6 months	9.3		
First-line regimen			
GP	9.1	0.626	NA
TP	7.4		
OT	7.8		

CR/PR, complete response/partial response; SD, stable disease; PD, progressive disease; GP, gemcitabine + platinum; TP, taxane + platinum; OT, other therapies; and NA, not available.

docetaxel (Taxotere, Sanofi-Aventis, Bridgewater, NJ, USA) in the second-line setting were previously published [13]. Briefly, all patients had confirmed stage III or IV NSCLC; had received no more than one prior chemotherapy regimen for the treatment of advanced disease; had an ECOG PS of zero to two; were ≥18 years of age, with measurable or evaluable disease; and had adequate bone marrow, hepatic, and renal function. Exclusion criteria included the following: prior docetaxel or pemetrexed treatment, significant weight loss (≥10% body weight during the previous 6 weeks), ≥ grade 3 peripheral neuropathy, symptomatic or uncontrolled brain metastases, uncontrolled pleural effusions, or an inability to interrupt nonsteroidal anti-inflammatory drugs. All patients provided written informed consent before treatment. The protocol was approved by each institution's ethical review board.

From March 2001 through February 2002, 571 patients were randomly assigned to receive either docetaxel 75 mg/m^2 (n = 288) or pemetrexed 500 mg/m^2 (n = 283) every 3 weeks. All 571 patients were assessable for survival and TTP analyses; 538 patients qualified for objective tumor response evaluation. Time elapsed since first-line therapy was available on 563 patients and PS at start of second-line therapy was available on 538 patients. Best response rate to first-line treatment was available on 545 patients and used the reported data collected at study entry and did not undergo independent radiologic confirmation.

Table 3. Summary of overall survival time subgroup analyses

Subgroup	GP MST	TP MST	OT MST	Treatment *P* value	Subgroup by treatment interaction *P* value
Gender					
Female	9.9	7.9	9.6	0.159	0.535
Male	8.4	5.8	7.2	0.620	
Age[a]					
<70	9.1	7.0	7.5	NA	NA
≥70	8.8	9.1	8.8		
Stage					
III	13.0	8.0	9.0	0.137	0.346
IV	8.7	7.4	6.7	0.748	
Histology					
Adenocarcinoma	9.5	7.8	8.8	0.164	0.713
Squamous cell carcinoma	7.65	7.4	6.0	0.701	
Other/mixed	8.8	5.8	7.9	0.984	
Performance status					
0	10.1	10.5	13.7	0.128	0.275
1	9.1	7.8	7.7	0.670	
2	3.7	2.0	2.6	0.116	
Best overall response					
CR/PR	18.5	12.4	13.3	0.679	0.714
SD	10.2	9.9	10.8	0.765	
PD	4.2	5.2	4.8	0.579	
Time to first line					
≤3 months	8.3	6.2	6.4	0.570	0.925
3–6 months	9.2	7.5	7.8	0.740	
≥6 months	9.8	8.4	9.3	0.374	

[a]Age was not further examined for interaction in a subgroup analysis since the factor was not significantly associated with increased survival in the Cox proportional hazards model.
GP, gemcitabine + platinum; TP, taxane + platinum; OT, other therapies; MST, median survival time in months; NA, not available; CR/PR, complete response/partial response; SD, stable disease; and PD, progressive disease.

statistical analysis

The retrospective statistical analysis compared the survival data for all patients combined and each of the three first-line treatment groups from the randomized, phase III, advanced NSCLC study based on first-line therapy received: gemcitabine + platinum (GP) (n = 182), taxane + platinum (TP) (n = 113), and other therapies (OT) (n = 276). The OT group consisted of vinorelbine + platinum (35%), etoposide + platinum (19%), gemcitabine + vinorelbine (11%), and other regimens (35%).

In the phase III study, the efficacy measures of pemetrexed and docetaxel were similar. There was no interaction between the first-line therapies and the second-line therapy. Therefore, the outcome data for these two treatment groups were pooled for this analysis. Unless otherwise stated, all tests of hypotheses were conducted at the $\alpha = 0.05$ level, with a 95% CI.

Cox proportional hazards model was used for the comparison of survival and TTP (data not shown) among the first-line therapies in baseline characteristics, subgroups when applicable (e.g. age and gender), and treatment and subgroup by treatment interaction. Both unadjusted and adjusted comparisons for the predictors were analyzed for survival. Kaplan–Meier estimates were used to assess medians and percentiles. Comparison of the tumor response rates among the first-line therapies

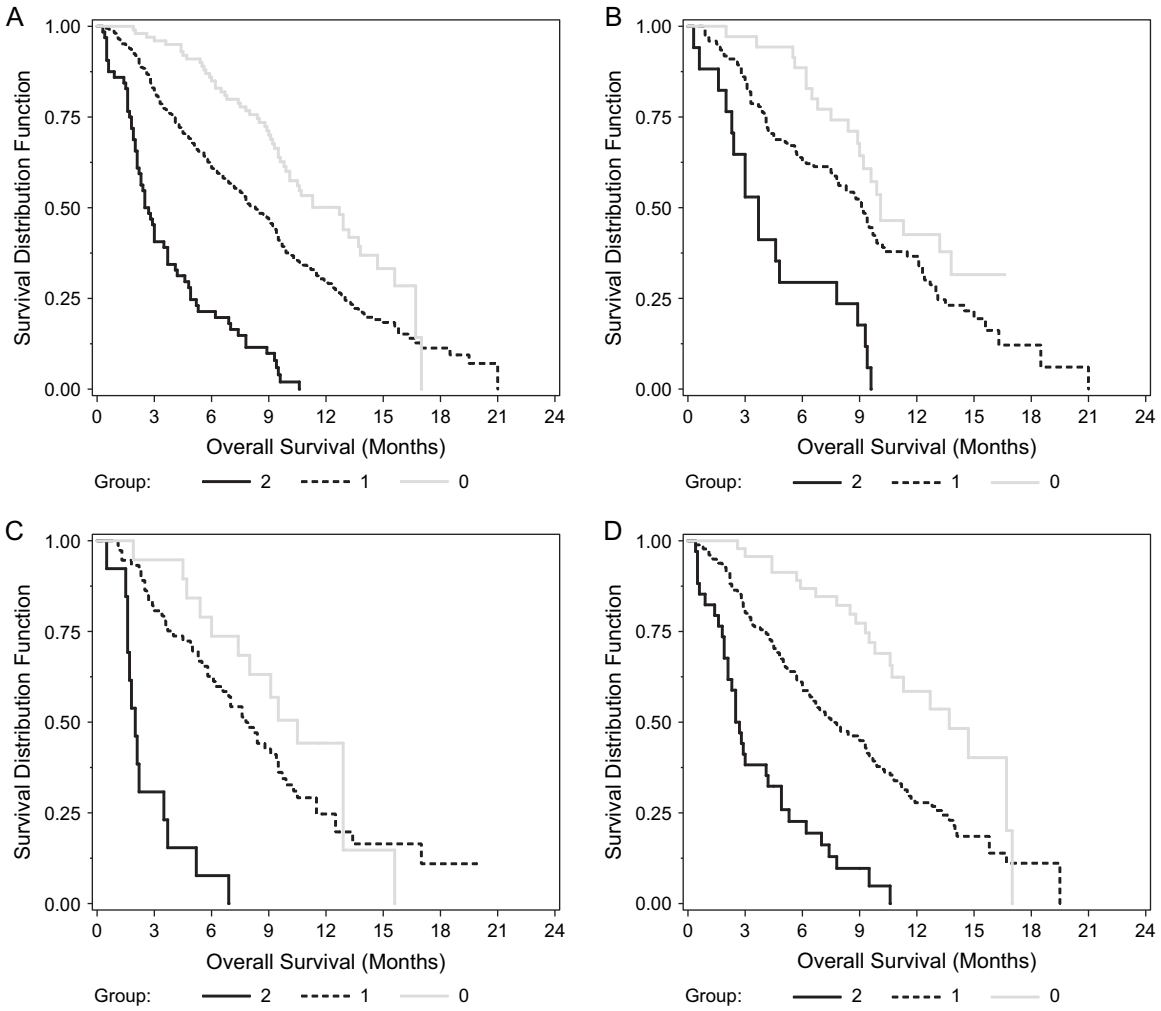

Figure 1. Survival by performance status at the start of second-line therapy. **(A)** Entire population, **(B)** gemcitabine + platinum, **(C)** taxane + platinum, and **(D)** other therapies.

was made using the Fisher's exact test with 95% CI calculated using the method of Leemis and Trivedi [15].

results

Baseline characteristics are shown in Table 1. Median survival by baseline characteristics with univariate and multivariate analysis is shown in Table 2. Median survival by baseline characteristics and treatment group is shown in Table 3.

age

The median age was 58 (range 22–87) in the entire patient population and 57 (range 22–79), 58 (range 40–87), 59 (range 30–81) in the GP, TP, and OT groups, respectively ($P = 0.177$) (Table 1). Age was not a significant prognostic factor [16]. Patients who were elderly (≥70 years old) had a median survival of 8.8 months compared with 7.9 months for those <70 years ($P = 0.809$) (Table 2).

gender

There were 411 (72%) males and 160 (28%) females in the entire group. In the GP, TP, and OT groups, there were 71%, 59%, 78% males, respectively ($P < 0.001$) (Table 1). TP had significantly more women than the other two groups. Gender was a significant prognostic factor as the median survival for females was 9.4 months versus 7.2 months for males ($P = 0.001$) (Table 2).

stage at diagnosis

There were 144 (25%) with stage III disease and 427 (75%) with stage IV disease at diagnosis for the entire population. In the GP, TP, and OT groups, there were 82%, 77%, and 69% with stage IV disease at diagnosis, respectively ($P = 0.008$) (Table 1). Stage at diagnosis was also a significant prognostic factor as the median survival for stage III disease at diagnosis was 9.5 months compared with 7.8 months for stage IV disease ($P = 0.036$) (Table 2).

histology

For the entire population, 296 (52%) had adenocarcinoma, 171 (30%) had squamous cell carcinoma, and 104 (18%) had other or mixed histology. In GP, TP, and OT groups, 53%, 63%, and 46% had adenocarcinomas, respectively

($P = 0.047$) (Table 1). TP had more adenocarcinoma histology than the other two groups. Histology was a significant prognostic factor as the median survival for patients with adenocarcinoma was 9.1 months, 6.5 months for squamous cell carcinoma, and 7.8 months for other or mixed histology ($P = 0.004$) (Table 2).

PS at start of second-line treatment

Of the 538 patients evaluated for PS, 100 (19%) had ECOG PS of zero, 374 (70%) had ECOG PS of one, and 64 (12%) had ECOG PS of two. [Unknown was not included in analyses ($n = 33$)]. For GP, TP, and OT, the percentages were similar ($P = 0.849$) (Table 1). PS was a significant prognostic factor. For all patients, median survival was 12.7 months for ECOG PS of zero, 8.3 months for ECOG PS of one, and 2.6 months for ECOG PS of two ($P < 0.001$) (Table 2). Figures 1A–D show OS based on PS for the entire population, GP, TP, and OT, respectively.

best overall response to first-line treatment

For the whole study population, best responses to first-line therapy were 16 (3%) complete response (CR), 190 (35%) partial response (PR), 199 (37%) stable disease (SD), and 140 (26%) progressive disease (PD). The objective response rate was 41% for GP, 35% for TP, and 37% for OT ($P = 0.714$) (Table 1). The disease control rate (CR/PR + SD) was 76% for GP, 76% for TP, and 72% for OT. Initial response to chemotherapy was a significant prognostic factor. For all patients, median survival was 15.8 months for CR/PR, 10.5 months for SD, and 4.6 months for PD ($P < 0.001$) (Table 2). Figures 2A–D show OS based on best response to first-line therapy for the entire population, GP, TP, and OT, respectively.

time elapsed from first- to second-line therapy

Patients were analyzed on the basis of time elapsed from first- to second-line therapy and grouped as ≤3 months, 3–6 months, and ≥6 months. Time elapse to initiation of second-line therapy for the study population was 277 (49%) ≤3 months, 117 (21%) 3–6 months, and 169 (30%) ≥6 months elapse to initiation of second-line therapy. Time since initial chemotherapy was a significant prognostic factor as median survival was 6.9 months, 9.2 months, and 9.3 months for ≤3 months, 3–6 months, and ≥6 months groups, respectively ($P = 0.001$)

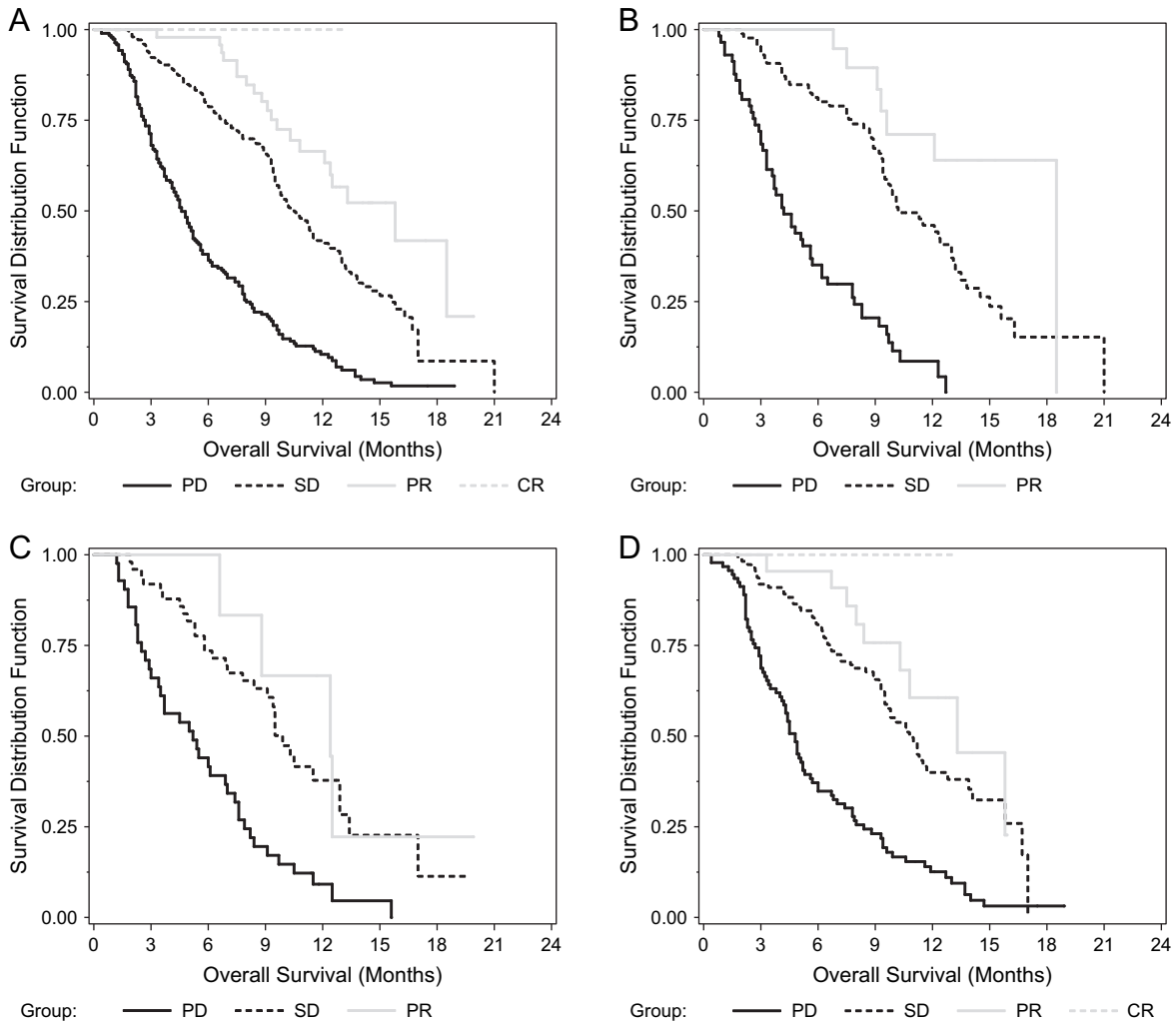

Figure 2. Survival by best overall response to first-line therapy. (**A**) Entire population, (**B**) gemcitabine + platinum, (**C**) taxane + platinum, and (**D**) other therapies.

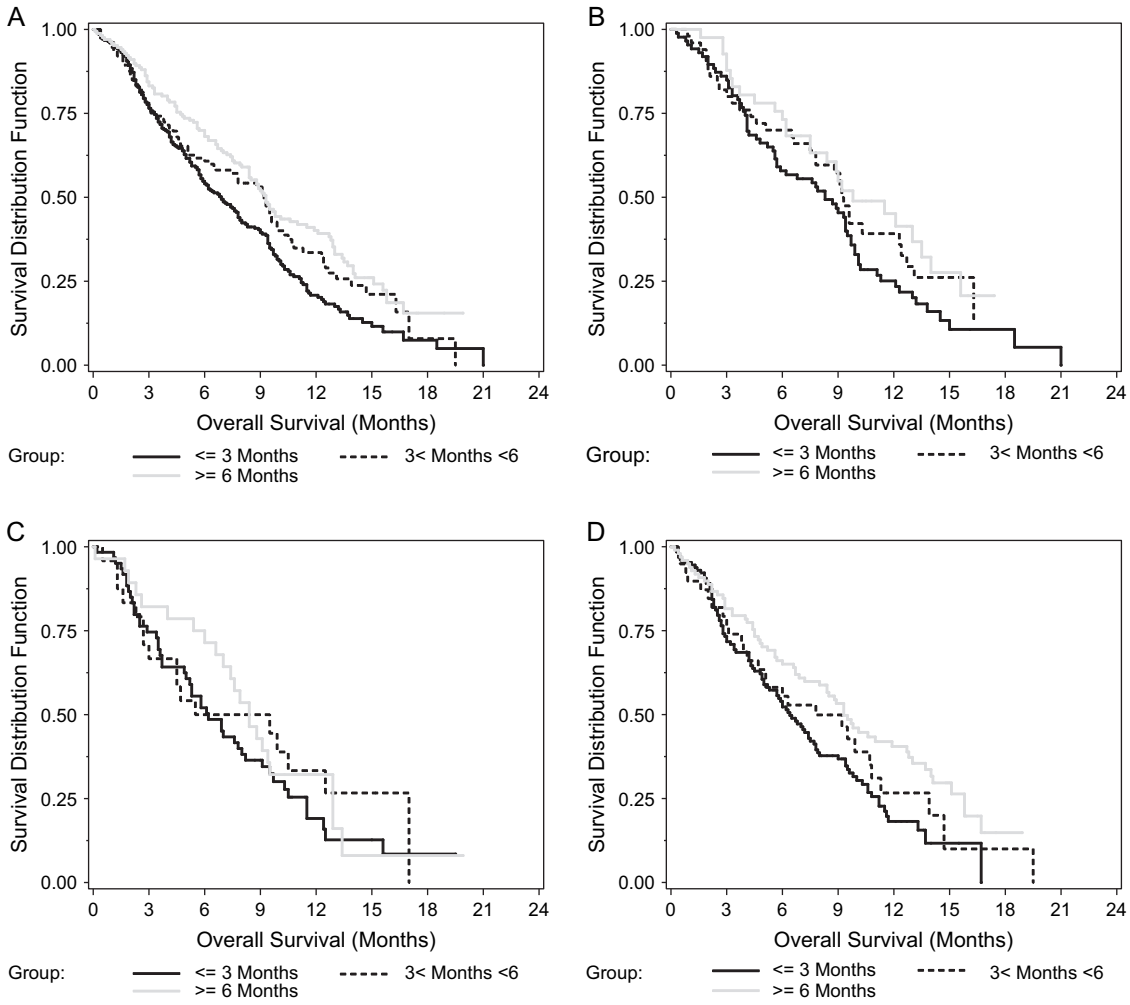

Figure 3. Survival by time elapsed from first- to second-line therapy. (**A**) Entire population, (**B**) gemcitabine + platinum, (**C**) taxane + platinum, and (**D**) other therapies.

(Table 2). Figures 3A–D show OS based on time elapsed from first- to second-line therapy for the entire population, GP, TP, and OT, respectively.

first-line regimen

Of the 571 patients randomly assigned and treated in the second-line study, 182 patients received GP, 113 received TP, and 276 received OT for first-line treatment. Patients treated with first-line GP had a numerically superior MST (9.1 months) relative to TP (7.4 months) or OT (7.8 months), but these differences failed to reach statistical significance ($P = 0.626$) (Table 2 and Figure 4).

Thus, by univariate analyses the following characteristics significantly influenced OS as follows: gender, stage at diagnosis, histology, PS, best overall response to first-line therapy, and time elapsed from first- to second-line therapy (Table 2). By multivariate analysis, the following characteristics significantly influenced OS as follows: gender, stage at diagnosis, PS, and best overall response to first-line therapy (Table 2).

In Table 3, the analysis of the subgroups within the baseline characteristics by treatment (GP, TP, or OT) did not demonstrate significant interaction. For each subgroup, there were no significant median OS differences by treatment group.

discussion

In this randomized trial comparing pemetrexed with docetaxel in the second-line setting of advanced NSCLC, we found that the following variables were associated with survival outcome: gender, histology, stage at diagnosis, PS at start of second-line therapy, type of initial therapy, best response to initial therapy, and time since initial therapy. Of these, type of initial therapy was not statistically significant in univariate analysis, while the following factors were statistically significant by multivariate analyses: gender, stage at diagnosis, PS at start of second-line therapy, and best response to initial therapy. Thus, these four factors should be used as stratification factors in future randomized trials. It should be noted that interpretation of best

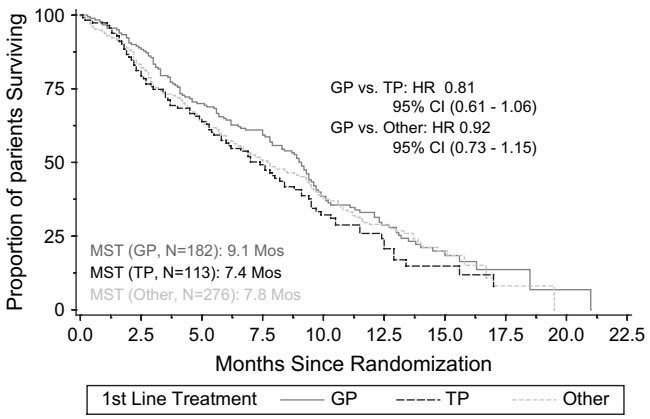

Figure 4. Overall survival based on first-line treatment.

response to first-line therapy by imaging was not confirmed in a standardized fashion. It is not surprising that status and gender have a significant impact on survival [17–18]. Appetite and weight loss have been reported as prognostic factors in the first-line setting [17], however, this data is not available for our analyses.

Other factors that should be documented when enrolling patients on trials are tumor histology and time elapsed from first- to second-line therapy. In the phase III study, the time elapse groups were divided into <3 or ≥3 months. In this analysis, the time elapse groups were further divided (≤3, 3–6, and ≥6 months). While there was significant survival improvement with longer time elapse by univariate analysis, this trend did not persist in the multivariate analysis. Smoking history in pack-years was not available in our data, but would be of interest when enrolling patients into trials beyond first-line therapy to see if this is an independent prognostic factor.

This retrospective analysis is the first to show the potential influence of first-line chemotherapy on the outcome of second-line cytotoxic chemotherapy. First-line therapy with GP has a numerically higher survival time compared with TP or OT. This outcome was similar regardless of best response to first-line treatment or length of time since discontinuing therapy.

To our knowledge, the effect of first-line chemotherapy on outcomes using targeted chemotherapy in advanced NSCLC has not been previously published. As more randomized trials are designed to answer treatment options in second-line therapy and beyond, conducting subset and retrospective analyses will help guide future study and hypotheses. Three additional areas that may be worth pursuing in data collection would be quality-of-life (QoL) improvement, and toxicity patients experienced within the first-line setting prior to enrollment in a second-line or beyond chemotherapy trial. Larger numbers of patients would have to be pooled to look for trends, but results of analysis might shed light on toxicity-prone individuals or profiles of patients most likely to benefit by QoL improvement despite poor prognostic factors or PS.

In conclusion, future trials in the second-line setting should stratify patients by gender, stage at diagnosis, PS at start of second-line therapy, and best response to first-line therapy. Advanced NSCLC patients have several first-line chemotherapy options. Selection of the most appropriate agents should be discussed with the treating physician.

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