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Possible differential EGFR-TKI efficacy among exon 19 deletional locations in *EGFR*-mutant non-small cell lung cancer

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ABSTRACT

Background: Exon 19 deletion mutations (Del-19s) and the exon 21 L858R point mutation are the most common epidermal growth factor receptor (EGFR) mutations. In Del-19, several subtypes actually exist, consisting of the deletional location with or without amino acid insertion/substitution. Little evidence has been described whether the Del-19 subtype affects EGFR-tyrosine kinase inhibitor (TKI) efficacy.
Methods: Between December 2005 and July 2012, we investigated 105 patients harboring a Del-19 who had received EGFR-TKIs. Efficacies of EGFR-TKIs such as response rate (RR), progression-free survival (PFS), and overall survival (OS) were retrospectively evaluated among various patient characteristics.
Results: Among these 105 patients with Del-19s, 78 (74%) patients had a deletion from E746 (Del-E746), and 27 (26%) exhibited a deletion from L747 (Del-L747). Median PFS of Del-E746 (11.7 months, 95% confidence interval [CI]: 9.3–15.6) was significantly longer than Del-L747 (10.0 months, 95% CI: 6.4–12.7) ($p = 0.022$). Insertions/substitutions were found in 19 patients (18%), and 91 patients (82%) were without insertions/substitutions. Median PFS without insertions/substitutions (11.7 months, 95% CI 9.3–15.2) was significantly longer than with insertions/substitutions (10.0 months, 95% CI: 4.0–10.6) ($p = 0.024$). No relationships were found for RR among all patient characteristics. In multivariate analysis, performance status (PS) (0/1 vs 2/3) and initial deletion site (Del-E746 vs Del-L747) were significant factors for longer PFS, whereas PS, gender (male vs female) and histology (adeno vs squamous) for longer OS.
Conclusions: Our data indicated better efficacy of EGFR-TKI in Del-E746 than Del-L747. Deletional locations may affect EGFR-TKI efficacy.

1. Introduction

Epidermal growth factor receptor (EGFR) gene mutation is the most established predictive factor for the efficacy of EGFR-tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib in patients with non-small cell lung cancer (NSCLC) [1,2]. Several types of *EGFR* mutation have been identified, and the most common mutations are exon 19 deletion mutations (Del-19s) and the L858R point mutation in exon 21. In the Japanese population literature, Del-19 is found in 48.2% of *EGFR*-mutant NSCLC and L858R in 42.7% [3]. EGFR-TKIs are sensitive for NSCLC with these mutations, and the response rate (RR) and progression-free survival (PFS) are 60–80% and 9–13 months, respectively [4–8]. Several phase III randomized clinical trials have proven that advanced *EGFR*-mutant NSCLC patients treated with EGFR-TKIs as first-line therapy obtained a longer progression-free survival than those on platinum-based standard chemotherapy [5–8]. Sensitivity to EGFR-TKIs differs among types of *EGFR* mutations [3], and several reports have documented the possibility that Del-19 is associated with more effective EGFR-TKI therapy than L858R [9,10].

Concerning Del-19, several different deletion and insertions/substitutions have been identified in *EGFR*-mutant NSCLC. In-frame deletions of exon 19 encompassing the amino acids from codons E746 to A750 (designated as the ELREA fragment) or L747 to E749 (the LRE fragment) constitute the most common mutations. According to the "Somatic Mutations in *EGFR* Database (SMEGFR-DB)", the most frequent Del-19s are delE746-A750 (28.89%), followed by delL747-P753insS (2.49%) and delL747-A750insP

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(1.73%) [11]. However, there is little evidence whether different Del-19s are associated with different therapeutic responses and clinical outcomes under EGFR-TKI therapy. The aim of our study was to investigate whether the efficacy of EGFR-TKI differs according to the subtype of Del-19 in *EGFR*-mutant NSCLC.

2. Patients and methods

2.1. Patients

From December 2005 to July 2012, we screened 113 NSCLC patients harboring Del-19 at Kobe City Medical Center West Hospital, Institute of Biomedical Research and Innovation, and Kobe City Medical Center General Hospital. Patients' results were analyzed using medical and radiographic records to take age, gender, smoking history, Eastern Cooperative Oncology Group (ECOG), performance status (PS), clinical stage and histology into account. Patients were treated with EGFR-TKIs (gefitinib and erlotinib). Since our study was a retrospective observational cohort and included no therapeutic intervention, written informed consent was waived.

2.2. Tumor specimens and EGFR mutation analysis

Tumor specimens were obtained by various methods: ultrasound or computed tomography (CT)-guided needle biopsy, bronchoscopic transbronchial biopsy, cell blocks of malignant effusions, and surgical tissues. We isolated tumor DNA from these specimens, and *EGFR* mutations were analyzed using the peptide nucleic acid–locked nucleic acid PCR clamp method [12].

2.3. Evaluation of EGFR-TKI efficacy

The initial doses of gefitinib and erlotinib were 250 mg/day and 150 mg/day, respectively. Each drug was orally administered once a day until progressive disease (PD) or unacceptable toxicity was noted. Dose reduction or interruption was undertaken in the case of toxicity. Chest radiography was performed every 1–4 weeks and chest CT scans every 1–3 months to evaluate treatment response and disease progression. Tumor response was retrospectively evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1. The duration of PFS was calculated from the date of initiation of EGFR-TKI treatment to the date of disease progression or death. Overall survival (OS) time was determined from the date of initiation of EGFR-TKI treatment to the date of death or the last follow up on July 31, 2012.

2.4. Statistical analysis

PFS and OS were estimated by the Kaplan–Meier method. Independent risk factors were assessed in multivariate analysis using the Cox proportional hazards model. A backward stepwise approach was adopted to select the variables for multivariate analyses. A p-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using JMP 9 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Between December 2005 and July 2012, 113 patients with NSCLC harboring Del-19 were treated with EGFR-TKI. Eight patients with indeterminate Del-19 subtype were excluded from the study, thus the present retrospective analysis included 105 patients. Their clinical characteristics are shown in Table 1. The median age was 67.0 years (range, 30–90 years). Most patients were female (60.0%), had never smoked (61.9%) and had a good PS of

Table 1
Characteristics of patients harboring exon 19 deletions.

Characteristics	No. of patients (n = 105)	%	Initial deletion site		
			E746	L747	p-value
Age (years)					
Median (range)	67.0 (30–90)				
<70	62	59%	47	15	0.669
≥70	43	41%	31	12	
Gender					
Male	42	40%	29	13	0.319
Female	63	60%	49	14	
Smoking history					
Never	65	62%	48	17	0.895
Ever	40	38%	30	10	
PS (ECOG)					
0/1	83	79%	61	22	0.791
2/3	22	21%	17	5	
Stage					
IIIB/IV	85	81%	62	23	0.585
Recurrence	20	19%	16	4	
Histology					
Adenocarcinoma	99	94%	73	26	0.585
Squamous cell carcinoma	6	6%	5	1	
EGFR-TKI					
Gefitinib	88	84%	65	23	0.821
Erlotinib	17	16%	13	4	
EGFR-TKI administration					
First-line	47	45%	33	14	0.391
Second-line or later	58	55%	45	13	
Initial deletion site					
E746	78	74%			
L747	27	26%			
Insertion mutation					
With	19	18%	2	17	<.0001
Without	86	82%	76	10	

PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

Table 2
Subtypes of exon 19 deletions ($n = 105$).

Deletion	Insertion/substitution	Number (%)
Deletions from E746		
E746-A750		76(72.3%)
E746-R748	E749G, A750P	1(1.0%)
E746-T751	S752V, P753S	1(1.0%)
Deletions from L747		
L747-T751		8(7.6%)
L747-S752	E746V	6(5.6%)
L747-E749	A750P	4(3.8%)
L747-S752	P753S	4(3.8%)
L747-S752		2(1.9%)
L747-A750	T751P	1(1.0%)
L747-S752	P753Q	1(1.0%)
L747-S752	P753S, A755G	1(1.0%)

0/1 (79.0%). Adenocarcinoma (94.3%) were predominant. EGFR-TKIs were administered on and after second-line chemotherapy (55.2%). Gefitinib was the principal EGFR-TKI used (83.8%). Sorted between Del-E746 and Del-L747, there were no significant differences in patient characteristics. On another front, E746 deletions were rarely accompanied by insertion mutation, while L747 deletions often were.

3.2. Subtypes of exon 19 deletion mutation

Del-E746 was present in 78 patients (74%), and Del-L747 in the remaining 27 (26%), whereas insertions/substitutions were also seen in 19 patients (18%). The most frequent Del-19s were delE746-A750 (72.3%), followed by delL747-T751 (7.6%). The most frequent insertion mutation was E746V in L747-S752 (6 patients, 5.6%) (Table 2).

3.3. Tumor response and survival

Analyses of response rates (RRs), PFS and OS are shown in Table 3. The overall RR to EGFR-TKIs was 51.9%, with no significant correlations with any clinical factors. RRs were 53.8% and 44.4% in the Del-E746 and Del-L747 groups, respectively ($p = 0.37$). For patients with insertions/substitutions, the RR was 52.6%, compared with 51.2% when none was present ($p = 0.95$).

The median PFS of all patients was 10.2 months. The median PFS was significantly longer for patients in the Del-E746 group (11.7 months, 95% CI: 9.3–15.6) than for Del-L747 patients (10.0 months, 95% CI: 6.4–12.7) ($p = 0.022$) (Fig. 1A). The median PFS was also 11.7 months for patients without insertions/substitutions (95% CI: 9.3–15.2) and 10.0 months in those with (95% CI 4.0–10.6) ($p = 0.024$) (Fig. 2A). In the univariate analysis, good PS, administration on second-line or later, Del-E746, and absence of insertions/substitutions were identified as likely predictive factors for longer PFS.

The median OS of all patients was 40.9 months, broken down as 47.4 months in the Del-E746 group (95% CI: 26.9–55.1) and 31.5 months in the Del-L747 group (95% CI: 17.0–37.0) ($p = 0.855$) (Fig. 1B). The median OS was 47.4 months for patients without insertions/substitutions (95% CI: 26.9–55.8) and 23.2 months in those with (95% CI: 16.5–39.5) ($p = 0.439$) (Fig. 2B). In the univariate analysis, good PS, adenocarcinoma histology, and EGFR-TKI administration on second-line or later were identified as likely predictive factors for longer OS.

Efficacy of gefitinib vs erlotinib was not recognized as a significant difference.

3.4. Relapse patterns

In this study, 90 patients relapsed totaling 116 incidences. Some patients had multiple metastases (Table 4). Recurrences in CNS

Table 3
Univariate analyses of response rate, progression-free survival and overall survival.

Characteristics	RR	p-value	PFS	p-value	OS	p-value
All patients ($n = 105$)	51.9%		10.2		40.9	
Age (years)						
<70	50.0%	0.633	10.2	0.792	50.2	0.162
≥70	54.8%		10.1		40.9	
Gender						
Male	48.8%	0.605	9.3	0.315	23.7	0.178
Female	54.0%		12.7		50.2	
Smoking history						
Never	56.9%	0.188	11.7	0.375	40.9	0.116
Ever	43.6%		9.3		23.7	
PS (ECOG)						
0/1	54.8%	0.178	12.7	<0.0001	50.2	<0.0001
2/3	40.9%		6.0		11.4	
Stage						
IIIB/IV	53.6%	0.330	9.8	0.124	32.0	0.358
Recurrence	45.0%		21.2		50.2	
Histology						
Adenocarcinoma	52.0%	0.624	10.5	0.171	40.9	0.0082
Squamous cell carcinoma	50.0%		6.8		10.2	
EGFR-TKI						
Gefitinib	51.1%	0.460	10.1	0.285	40.9	0.898
Erlotinib	56.3%		12.7		NR	
Administration of EGFR-TKI						
First-line	56.5%	0.403	9.6	0.022	23.2	0.012
Second-line and later	48.3%		14.9		55.1	
Initial deletion site						
E746	53.8%	0.366	11.7	0.022	47.4	0.855
L747	44.4%		10.0		31.5	
Insertion mutation						
With	52.6%	0.946	10.0	0.024	23.2	0.439
Without	51.2%		11.7		47.4	

RR, response rate; PFS, progression-free survival; OS, overall survival; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, Epidermal growth factor receptor-tyrosine kinase inhibitor; NR, not reached.

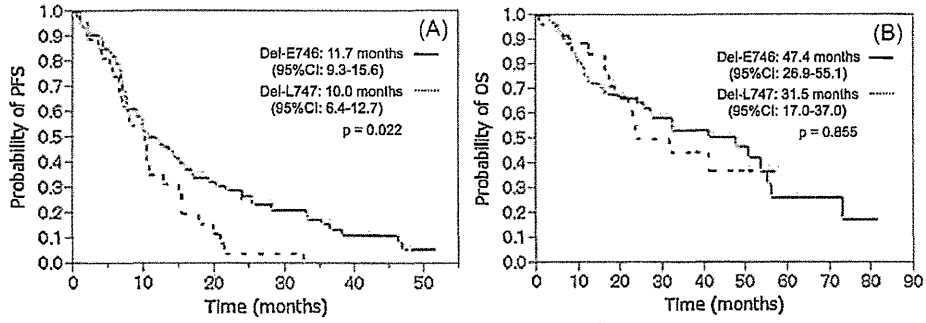

Fig. 1. Comparison of progression-free survival (A) and overall survival (B) between Del-E746 and Del-L747.

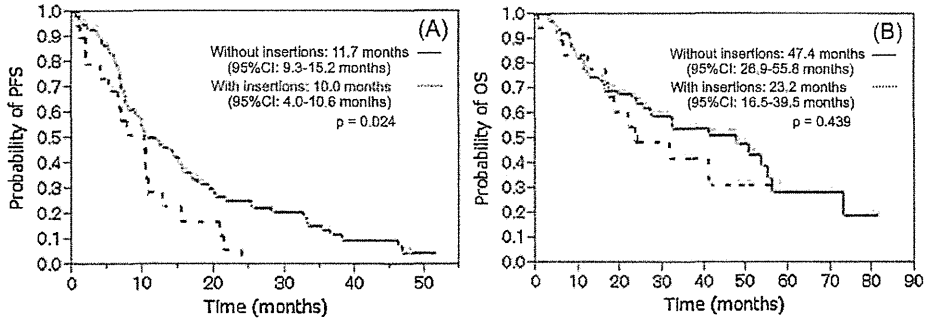

Fig. 2. Comparison of progression-free survival (A) and overall survival (B) with insertions/substitutions or without.

were common relapse patterns as expected in EGFR-TKI administration. There was no significant difference in relapse patterns between E746 and L747.

3.5. Multivariate analysis

Multivariate analyses were performed to identify independent risk factors using the Cox proportional hazards model. A backward stepwise approach was adopted to select the variables for multivariate analyses.

In the multivariate analysis using a proportional hazards model, good PS and Del-E746 remained as identified independent predictive factors for longer PFS (Del-E746: hazards ratio: 0.698, 95% CI: 0.549–0.897, $p = 0.0056$) (Table 5).

Multivariate analysis of OS identified only good PS, female and adenocarcinoma histology as significant factors (Table 4). However, neither the initial deletion site, nor the insertions/substitutions were significant prognostic factors for OS in multivariate analysis.

4. Discussion

We found that EGFR-TKIs were more effective against NSCLCs with Del-E746 than those with Del-L747, which was also verified by multivariate analysis. These results may indicate that deletional locations affect EGFR-TKI efficacy. A few reports have focused on the influence of different Del-19s on EGFR-TKI efficacy [13–16]. Consistent with our data, Lee et al. [13] also demonstrated that the efficacy of EGFR-TKI was better in Del-E746 than Del-L747 (median PFS: 14.2 vs 6.5 months, $p = 0.021$). Meanwhile, two of these reports showed that the efficacy of EGFR-TKI in Del-E746 was similar to Del-L747 [14,15]. On the other hand, Costa et al. [16] found that the efficacy of erlotinib in patients with non-ELREA Del-19 was greater than in those with ELREA Del-19. In contrast to the report from Costa et al., Chung et al. [14] exhibited that the efficacy of EGFR-TKIs in patients with LRE Del-19 was greater than in those with non-LRE Del-19. The reasons for these potential discrepancies are not clear, but the conclusions are controversial. Notably, Del-E746 is much more common than Del-L747 in all these

Table 4
Major relapse patterns.

PD pattern	Relapse site	No. of incidences ($n = 116$)	%	Initial deletion site		
				E746 ($n = 78$)	L747 ($n = 27$)	p-value
Intrathoracic	Primary	32	28			
	Pleural effusion	18	16	46 (54.8%)	16 (50.0%)	0.646
	Lung	12	10			
CNS	Brain	21	18	20 (23.8%)	8 (25.0%)	0.894
	Leptomeninges	7	6			
Extrathoracic	Bone	11	9			
	Liver	8	7			
	Lymph node	5	4	18 (21.4%)	8 (25.0%)	0.683
	Adrenal gland	1	1			
	Small intestine and peritoneum	1	1			

PD, progressive disease; CNS, central nervous system. Some patients had multiple metastases.

Table 5
Multivariate analyses of progression-free survival and overall survival.

Covariate	Hazard ratio	95% CI	*p*-value
Progression-free survival			
ECOG PS (0/1 vs 2/3)	0.538	0.409–0.720	<0.0001
Stage (IIIB/IV vs recurrence)	1.190	0.915–1.590	0.201
Histology (adeno vs squamous)	0.702	0.477–1.136	0.137
Initial deletion site (E746 vs L747)	0.698	0.549–0.897	0.006
Overall survival			
Age (≥70 vs <70)	1.322	0.968–1.811	0.079
Gender (female vs male)	0.748	0.559–0.999	0.049
ECOG PS (0/1 vs 2/3)	0.471	0.339–0.668	<0.0001
Histology (adeno vs squamous)	0.440	0.277–0.768	0.006

ECOG, Eastern Cooperative Oncology Group; PS, performance status; CI, confidence interval.

studies. According to the Somatic Mutations in Epidermal Growth Factor Receptor DataBase (SM-EGFR-DB) [11], the most frequent Del-19s are delE746-A750 (28.89%), followed by delL747-P753insS (2.49%) and delL747-A750insP (1.73%). Among Del-19s, delE746-A750 (Del-E746) is usually predominant, as in our cohort. Some studies showed that EGFR-TKIs exhibited superior efficacy against Del-19 than L858R [9,10], while other reported similar efficacies between Del-19 and L858R [5,6]. To our knowledge, there are no reports showing poorer EGFR-TKI efficacy in patients with Del-19, compared with other *EGFR* mutations. Del-E746 is the predominant subtype of Del-19, and it is resonable that the efficacy of EGFR-TKI in patients with Del-E746 is better than in other subtypes.

Univariate analysis of our study demonstrated better efficacy of EGFR-TKI in patients harboring a Del-19 without insertions/substitutions than in those with insertions/substitutions (median PFS: 11.7 vs 10.0 months, $p=0.024$) (Fig. 2). Conversely, Lee et al. [13] reported longer PFS in patients harboring a Del-19 with insertions/substitutions than those without (median PFS: 22.4 vs 12.3 months, $p=0.012$). Unfortunately, multivariate analysis was unable to validate the result of univariate analysis, but insertions/substitutions in Del-19 may influence effectiveness of EGFR-TKI. We speculate that insertions/substitutions in Del-19 involve the molecular structure of the EGFR tyrosine kinase domain and/or affinity of EGFR-TKI and adenosine triphosphate (ATP) against the ATP binding pocket. Further studies are needed to elucidate whether insertions/substitutions in Del-19 affect EGFR-TKI efficacy.

Multivariate analysis of our study identified good PS, female and adenocarcinoma histology as significant factors for better OS. These are generally common prognostic factors in advanced NSCLC. Initial deletion site was not a significant factor for better OS, but median OS of Del-E746 was 47.4 months, whereas Del-L747 was 31.5 months ($p=0.855$). This difference was not statistically significant, but the survival curve of E746 is slightly higher than that of L747, and there were many censored cases. More mature data may prove survival advantage of E746, compared with L747. With regard to the data on with or without insertions/substitutions, we presume a similar consideration.

Our study has several limitations. First, it is retrospective. RR and PFS are very soft endpoints, and the interval for the restaging imaging was highly variable, representing a bias for PFS assessment. Second, the cohort is relatively small. Types and numbers of minor Del-19s were limited, and there were not any non-LRE Del-19s. Third, EGFR-TKIs were administered at second-line or later in more than half of patients (55%). In Japan, gefitinib as first-line chemotherapy was not available under Public Health Insurance until October 2011, which included the investigational period in this study. Erlotinib was also made available under Public Health Insurance as the first-line treatment from July of 2013. Therefore, patients given gefitinib as first-line chemotherapy during this period could not be approved for platinum doublet chemotherapy because of poor performance status. This selection bias would bias performance status, survivals, and skew our results. Efficacy of EGFR-TKI according to the lines of therapy was a recognized significant difference in the univariate analysis. However, the multivariate analysis did not identify the lines of therapy as a significant factor, and was probably confounded by performance status. Several reports demonstrated that efficacies of EGFR-TKIs are similar between first-line and second-line or later [17,18]. However, a limited data focus on the first-line setting would eliminate any potential biases, and more sophisticated results may be obtained to elucidate the difference of EGFR-TKI efficacy among subtypes of Del-19. Finally, this study would become a more meaningful study if we could examine each case's mechanism of resistance (acquired T790M, MET amplication, HGF, etc.) and discuss them. However, Japanese clinical practice does not often perform rebiopsy to examine resistance mechanisms. In addition, because it was difficult for many medical institutions to examine other resistant mechanisms such as MET amplification and HGF, we were not able to examine them in this study.

In conclusion, we found that EGFR-TKIs were more effective in *EGFR*-mutant NSCLC with Del-E746 than in those with Del-L747. Patients with Del-E746 had a significantly longer PFS than those with Del-L747, and this result was also verified by multivariate analysis. Deletional locations may affect EGFR-TKI efficacy.

Conflict of interest statement

The authors declare no conflict of interest.

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LETTER TO THE EDITOR

Successful Cetuximab Therapy After Failure of Panitumumab Rechallenge in a Patient with Metastatic Colorectal Cancer: Restoration of Drug Sensitivity After Anti-EGFR Monoclonal Antibody-Free Interval

Akito Hata · Nobuyuki Katakami · Naoto Kitajima

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To the editor:

We previously reported the efficacy of panitumumab rechallenge for chemorefractory metastatic colorectal cancer (mCRC) [1]. Interestingly, cetuximab combination therapy was also effective after the failure of panitumumab rechallenge in the present case. Anti-epidermal growth factor receptor (EGFR) monoclonal antibody (MoAb) exerted clinical benefit three times, due to anti-EGFR MoAb-free intervals. We herein describe the clinical course following the failure of panitumumab rechallenge.

After progression on panitumumab rechallenge with FOLFIRI, S-1 plus bevacizumab was prescribed. Although pulmonary metastases progressed gradually, the tumors showed indolent growth, and therapy was continued for 6 months. Six months after panitumumab cessation, we administered cetuximab (400 mg/m^2→250 mg/m^2 weekly) plus irinotecan (130 mg/m^2 biweekly). Pulmonary metastases responded to the therapy for 6 months (Figs. 1 and 2), and carcinoembryonic antigen decreased from 423.0 to 290.3 ng/ml. Skin rash and paronychia were mild, and the therapy was generally well tolerated. Following progression on cetuximab combination therapy, regorafenib is under administration.

Sensitivity to anti-EGFR MoAb was probably restored, by the 6-month anti-EGFR MoAb-free interval, from panitumumab cessation to cetuximab initiation. As we speculated in the previous paper [1], drug-free intervals can recover sensitivities to anti-EGFR MoAbs, regardless whether cetuximab or panitumumab. Santini et al. have reported the efficacy of cetuximab rechallenge [2]. They hypothesized that the drug-sensitive clones may regrow and become dominant over resistant clones during cytotoxic chemotherapies without an anti-EGFR MoAb, representing the heterogeneous existence of drug-sensitive and drug-resistant clones in an individual patient. Notably, pulmonary metastases of our patient exhibited a highly variable response, which included both responding and non-responding lesions (Figs. 1 and 2). This paradoxical response might imply drug-sensitive and drug-resistant clones heterogeneously existed in pulmonary metastases.

Anti-EGFR MoAb rechallenge can be a potentially good treatment option for chemorefractory patients with mCRC who respond to initial anti-EGFR MoAb, after an anti-EGFR MoAb-free interval. However, there is little evidence to elucidate its effectiveness, besides molecular alterations of the resistant mechanism, and the

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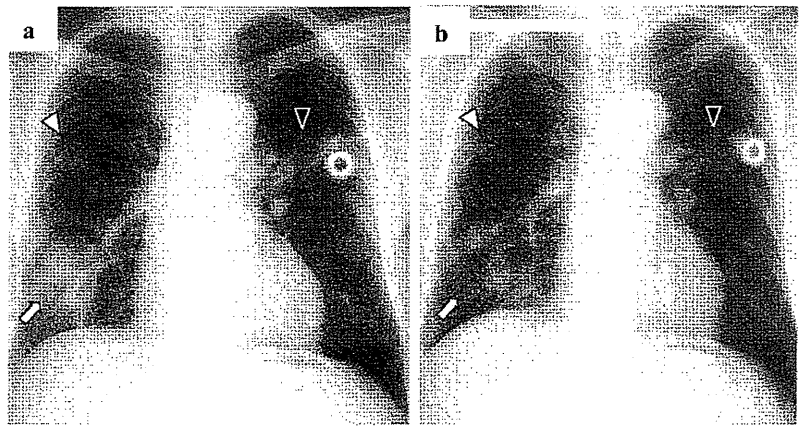

Fig. 1 **a** Chest X-ray before initiation of cetuximab combination therapy. **b** Two months after therapy. *Arrow* indicates a responding tumor; *black arrowhead* indicates a slightly responding tumor; *white arrowhead* indicates a slightly enlarging nodule

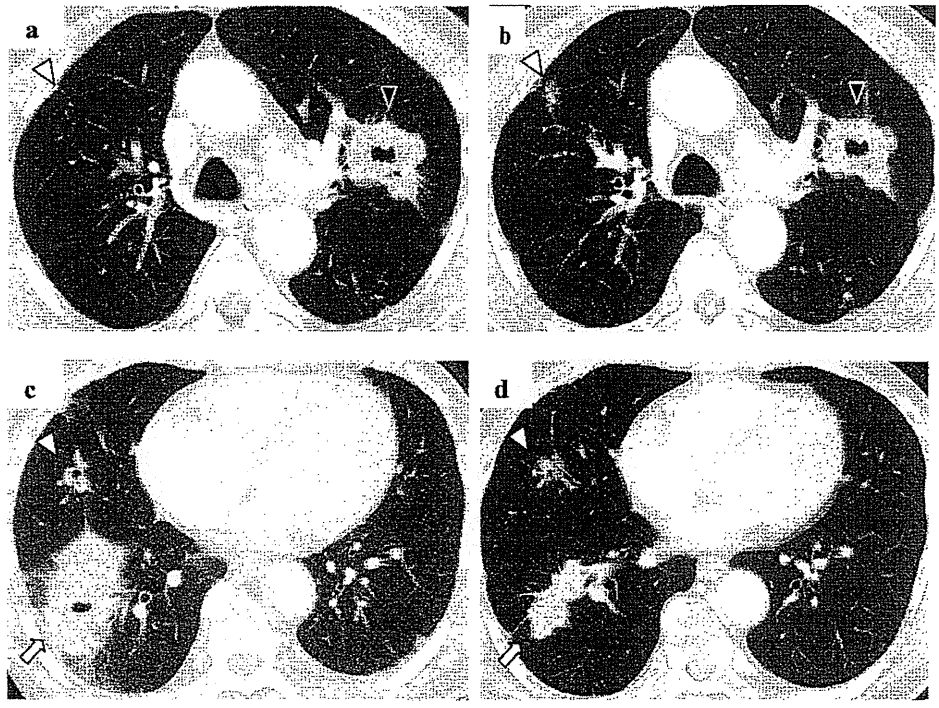

Fig. 2 **a**, **c** Chest computed tomography before initiation of cetuximab combination therapy. **b**, **d** Two months after therapy. *Arrow* indicates a responding tumor; *black arrowhead* indicates a slightly responding tumor; *white arrowhead* indicates slightly enlarging nodules

optimal length of anti-EGFR MoAb-free interval are unclear. Further investigations are warranted to evaluate prospectively the effectiveness of anti-EGFR MoAb re-challenge, and to clarify these unresolved questions.

Disclosure The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

A phase II study of pemetrexed in patients with previously heavily treated non-squamous non-small cell lung cancer (HANSHIN Oncology Group 001)

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Abstract
Purpose Pemetrexed has shown substantial activity in non-squamous non-small cell lung cancer (NSCLC) and is one of the current standard agents in second-line settings due to its efficacy and favorable tolerability profile. We conducted phase II study to evaluate the safety and efficacy of pemetrexed in Japanese patients with previously heavily treated, advanced non-squamous NSCLC.
Methods Patients with stage IIIB or IV non-squamous NSCLC, performance status (PS) 0–2, previous two to five regimens of chemotherapy were enrolled and received pemetrexed (500 mg/m^2) on day 1 every 21 days until disease progression. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety.
Results From August 2009 to May 2010, 46 patients were enrolled: median age 65 years; 52 % women; PS 0/1/2 26/67/7 %; previous treatment regimen 2/3/4/5 48/28/20/4 %; epidermal growth factor receptor activating mutation positive/wild/unknown 30/48/22 %. The median follow-up period was 13.5 months. The median number of treatment cycles was 4 (range 1–18 cycles). The median PFS was 5.2 months (95 % CI 3.0–5.8 months). The median OS was 14.4 months (95 % CI 9.4–21.3 months). The ORR was 8.7 % and DCR was 63.0 %. The grade 3/4 hematological adverse events include 8 patients with leukopenia, 11 with neutropenia, 5 with anemia, and 2 with thrombocytopenia. There were no reports of febrile neutropenia and no treatment-related death was observed.
Conclusion Treatment with pemetrexed in previously heavily treated Japanese non-squamous NSCLC patients is feasible and shows encouraging activity.

Keywords Pemetrexed · Non-small cell lung cancer · Heavily treated · Phase II

Clinical trials registration number UMIN ID: UMIN000002467.

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Introduction

Lung cancer is the most common cancer in the world, Japan included. Non-small-cell lung cancer (NSCLC) accounts for approximately 80–85 % of all cases of lung cancer. For previously untreated favorable patients with locally advanced or metastatic NSCLC, platinum-based chemotherapy offers a survival advantage over best supportive care alone. But most cases do eventually relapse.

Pemetrexed, docetaxel, and erlotinib are currently recommended as standard treatment for relapsed NSCLC. There are reports from several clinical studies being conducted as phase III trials for use in second-line treatment, including the JMEI study [1] comparing pemetrexed and docetaxel, TAX317 study [2] comparing docetaxel to placebo, and the TAX320 study [3] comparing docetaxel to vinorelbine or ifosfomide. There have also been reports of phase III trials of second- and third-line use, including the BR.21 study [4] on erlotinib and the V-15-32 study [5] comparing docetaxel and gefitinib. There are hardly any reports, however, of prospective studies on third-line use or beyond.

Pemetrexed is a novel multitargeted antifolate that inhibits three enzymes: thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, and it displays cytotoxic activity against several solid tumors including NSCLC [6].

Hanna et al. conducted a phase III study (JMEI study) comparing pemetrexed to docetaxel in second-line chemotherapy on relapsed advanced NSCLC patients previously treated with chemotherapy. While non-inferiority was not observed in the progression-free survival (PFS) (2.9 vs. 2.9 months) or overall survival (OS) (8.3 vs. 7.9 months) (hazard ratio = 0.99), there was also no report of a difference between pemetrexed and docetaxel [1]. The report cited the tendency of pemetrexed to display significantly milder toxicity than docetaxel in terms of grade 3 and 4 adverse events (AEs) such as neutropenia (5.3 vs. 40.2 %) and febrile neutropenia (1.9 vs. 12.7 %), elevating pemetrexed to a standard treatment for relapsed NSCLC as mildly toxic second-line chemotherapy.

Moreover, the clinical study findings on pemetrexed to date have suggested the possibility of histological efficacy differences [7], as it is recommended for use on non-squamous NSCLC.

Sun et al. conducted a clinical study on pemetrexed used alone in second-line or beyond on relapsed NSCLC. Seventy of the 100 patients received the drug in third-line or beyond. A comparison between second-line treatment and third-line treatment or beyond in terms of PFS did not show a significant difference, and they have not reported any difference in terms of toxicity [8]. The conclusion made from these findings is that pemetrexed is an effective regimen for third-line or beyond.

As there is little evidence on anticancer treatment third-line or beyond for NSCLC, we planned a phase II study on pemetrexed targeting this population.

Patients and methods

Patient eligibility

Patients with histologically or cytologically confirmed non-squamous NSCLC without large cell neuroendocrine carcinoma, classified as stage IIIB not amenable to curative treatment, stage IV or recurrent disease after surgery are the eligibility criteria included.

The main eligibility criteria were that administration of pemetrexed was as the third- to sixth-line of chemotherapy. Platinum doublet was not necessarily required as a prior treatment, and the contents of the previous treatment regimens were not specified. Neoadjuvant chemotherapy, adjuvant chemotherapy without UFT, S-1, gefitinib, and erlotinib were counted as one regimen. And the other eligibility criteria were as follows: measurable or evaluable disease; an Eastern Cooperative Oncology Group performance status (PS) of 0–2; older than 20 years; an estimated life expectancy of at least 3 months; and adequate bone marrow, renal and hepatic function.

Patients with prior pemetrexed treatment, interstitial pneumonia or pulmonary fibrosis detectable on computed tomography (CT) scan, uncontrolled pleural effusions, or symptomatic brain metastases were deemed ineligible.

The protocol was approved through institutional ethical review boards, and all patients were provided written informed consent before treatment.

The study was conducted in accordance with the ethical principles in the Declaration of Helsinki.

Treatment plan

Patients received 500 mg/m^2 of pemetrexed in a 10-min intravenous infusion on day 1 of a 21-day cycle. Cycles were repeated until disease progression, unacceptable toxicity, or until the patient or the investigator requested therapy discontinuation.

Patients were instructed to take 500 μg of folic acid orally every day, beginning approximately 1 week before the first dose of pemetrexed and continuing on a daily basis until 3 weeks after the last dose of pemetrexed. A vitamin B_{12} injection (1,000 μg) was intramuscularly administered approximately 1 week before the first dose of pemetrexed and was repeated approximately every 9 weeks until 3 weeks after the last dose of pemetrexed.

The subsequent cycles were begun if a patient presented a PS of 0–2, neutrophil count $\geq$1,500/μL, platelet count $\geq$75,000/μL, AST/ALT less than 2.5 times the upper limit of each facility, total bilirubin less than 1.5 times the upper limit of each facility, creatinine $\leq$1.5 mg/dL, and/or other non-hematologic toxicity of grade 2 or lower. A 3-week delay in initiating the subsequent course was allowed. Otherwise, the patient was withdrawn from the study. Patients were scheduled to receive pemetrexed until the administration was impossible.

In regard to dose modification of pemetrexed in the subsequent cycles, if, during the previous course, the patient presented grade 4 leukopenia, febrile neutropenia,

grade 4 thrombocytopenia, grade 3 or higher non-hematologic toxicity, or delay of starting a subsequent course by more than 30 days, the dose of pemetrexed was reduced to 400 mg/m^2. Any patients with grade 4 non-hematologic toxicities or grade 2 or higher interstitial pneumonia were withdrawn from the study. Patients received full supportive care.

Baseline and treatment assessments

The baseline assessment included a history and physical examination, complete blood count, comprehensive blood chemistries, and chest X-ray. CT scans of the chest and upper abdomen, magnetic resonance imaging (MRI) studies or CT scans of the brain, and bone scintigraphy or positron-emission tomography (PET)-CT studies were performed for tumor assessment within 28 days of initiation of the study treatment. Tumor measurements were assessed with a monthly CT scans. MRI studies of the brain was repeated every 3 months or on the appearance of any neurological symptoms. Objective tumor responses were based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. If a patient was documented as having a complete response (CR) or a partial response (PR), the respective response had to be confirmed 4 weeks later. A patient was considered to have stable disease (SD) if the response was confirmed and sustained for at least 6 weeks. PFS was defined as the time from enrollment to the date of confirmation of progressive disease (PD) or the date of death from any cause. OS was defined as the time from initial treatment to death from any cause. For patients of unknown death status, OS was censored at the last date the patient was known to be alive. Toxicity evaluations were based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Statistical analysis

In light of the previous data, we assumed that a median PFS time of 3 months in eligible patients would indicate potential usefulness, while a median PFS of 2 months would be the lower limit of interest. Based on the assumption, the number of patients needed to provide the 80 % power for a one-sided 0.05 level of type I error was calculated to be 37. Taking ineligible patients into account, the sample size was set at 45 in our study.

Descriptive statistics were analyzed to describe the baseline characteristics of the studied patients. Qualitative data are presented as numbers (%). We analyzed PFS and OS using the Kaplan–Meier method to estimate their median time points with 95 % confidence intervals.

Results

Patient characteristics

Forty-six patients were registered between September 2009 and May 2010. The median follow-up period was 13.5 months. Table 1 shows the baseline patient characteristics. The male/female ratio was virtually even, and only three patients had a PS of 2. Moreover, the percentages of smokers and non-smokers were virtually the same. 30 % of the patients were epidermal growth factor receptor (EGFR) mutation positive, 48 % were negative, and the mutation status was unknown for 22 %. 22 of the patients had undergone two previous treatment regimens (i.e., third-line), while 24 had undergone three to five previous treatment regimens (i.e., fourth- to sixth-line). The median number of treatment cycles was 4 (range 1–18 cycles). The median among third-line was 4 cycles. It was 6 cycles among fourth- to sixth-line. All 46 patients were deemed eligible for treatment, and all were evaluated for efficacy and safety. The observation period ended as of January 2012, effectively ending the study.

Efficacy

The median PFS was 5.2 months (95 % confidence interval (CI) 3.0–5.8 months) (Fig. 1a). The median PFS among third-line was 3.9 months (95 % CI 1.8–6.3 months). It was 5.6 months (95 % CI 1.7–7.3 months) (Fig. 2a) among fourth- to sixth-line. The medians among EGFR mutation positive and negative groups were 5.6 (95 % CI 2.6–7.3 months) and 4.2 months (95 % CI 1.7–8.6 months), respectively.

The median survival time (MST) was 14.4 months (95 % CI 9.4–21.3 months) (Fig. 1b). The MST among third-line was 12.3 months (95 % CI 6.1–21.3 months), and fourth- to sixth-line, 19.1 months (95 % CI 9.4–25.4 months) (Fig. 2b). Meanwhile, the medians among EGFR mutation positive and negative groups were 14.4 (95 % CI 9.1–20.2 months) and 20.5 months (95 % CI 6.0 months to not reached), respectively.

The response rate (RR) was 8.7 % and disease control rate (DCR) was 63.0 % (Table 2). While the RR and DCR among third-line were 4.5 and 59.1 %, respectively, they were 12.5 and 66.7 % among fourth- to sixth-line.

Toxicity

All registered cases were evaluated for AEs (Table 3). Regarding the frequency of AEs, no statistically significant difference was observed between the third-line and

Table 1 Patient characteristics

Characteristic	All lines ($n = 46$)	Third line ($n = 22$)	Fourth–sixth lines ($n = 24$)
Median age, years (range)	65 (49–82)	63 (49–82)	65 (51–82)
Gender, *n* (%)			
Female	24 (52.2)	10 (45.5)	14 (58.3)
Male	22 (47.8)	12 (54.5)	10 (41.7)
PS, *n* (%)			
0	12 (26.1)	5 (22.7)	7 (29.2)
1	31 (67.4)	16 (72.8)	15 (62.5)
2	3 (6.5)	1 (4.5)	2 (8.3)
Smoking status, *n* (%)			
Never	24 (52.2)	9 (40.9)	15 (62.5)
Ever	22 (47.8)	13 (59.1)	9 (37.5)
Stage, *n* (%)			
IIIB	7 (15.2)	4 (18.2)	3 (12.5)
IV	27 (58.7)	13 (59.1)	14 (58.3)
Post op	12 (26.1)	5 (22.7)	7 (29.2)
EGFR mutation status, *n* (%)			
Wild	22 (47.9)	11 (50.0)	11 (45.9)
Mutant	14 (30.4)	6 (27.3)	8 (33.3)
Unknown	10 (21.7)	5 (22.7)	5 (20.8)
No. of prior chemotherapy regimens, *n* (%)			
2	22 (47.8)	22 (100)	–
3	13 (28.3)	–	13 (54.2)
4	9 (19.6)	–	9 (37.5)
5	2 (4.3)	–	2 (8.3)

fourth- to sixth-line. The grade 3/4 hematological toxicities include 8 patients with leukopenia, 11 with neutropenia, 5 with anemia, and 2 with thrombocytopenia. While 2 patients required G-CSF, none of the patients required transfusion. Non-hematological toxicities: There were no reports of febrile neutropenia. While grade 4 dyspnea was observed in 3 cases, each case was deemed due to exacerbation of the original condition. Moreover, no treatment-related death was observed.

Subsequent treatment

Overall, 59.1 % (13/22) of third-line patients and 66.7 % (16/24) of fourth- to sixth-line patients received any subsequent treatment. Among the group of third-line, a total of 6 patients received a molecular targeted therapy by EGFR-TKI and a total of 25 patients received chemotherapy: 11 as single-agent, 3 as a doublet-agent, 11 as combination with bevacizumab. On the other hand, among the group of fourth- to sixth-line, a total of 6 patients received a molecular targeted therapy by EGFR-TKI and a total of 27 patients received chemotherapy: 11 as single-agent, 3 as a doublet-agent, 13 as combination with bevacizumab.

Discussion

This study was conducted on non-squamous NSCLC patients who have undergone many previous treatment regimens, as a majority has undergone three to five previous treatment regimens.

The median PFS, which was the primary endpoint, of our study was 5.2 months. The median PFS in the phase III studies used in comparison to assess the second-line treatments reported to date, i.e., JMEI and BR.21 studies were 2.9 and 2.2 months, respectively. This indicates the favorable outcome in our study. Moreover, the median PFS in the docetaxel group in a comparative phase III study in Japan, V-15-32 study, was shown to be 2.0 months. Once again, our study showed better results. The somewhat high median number of cycles in our study may have contributed to the favorable PFS, i.e., it was 4 cycles in the pemetrexed group in the JMEI study, 3 cycles in the docetaxel group in the TAX320 study, and 3 cycles in the docetaxel group in the V-15-32 study. Moreover, the high median number of cycles among fourth- to sixth-line was conceivably another reason.

At 14.4 months, the OS was quite favorable compared to the MST's in the JMEI, TAX320, and BR.21 studies

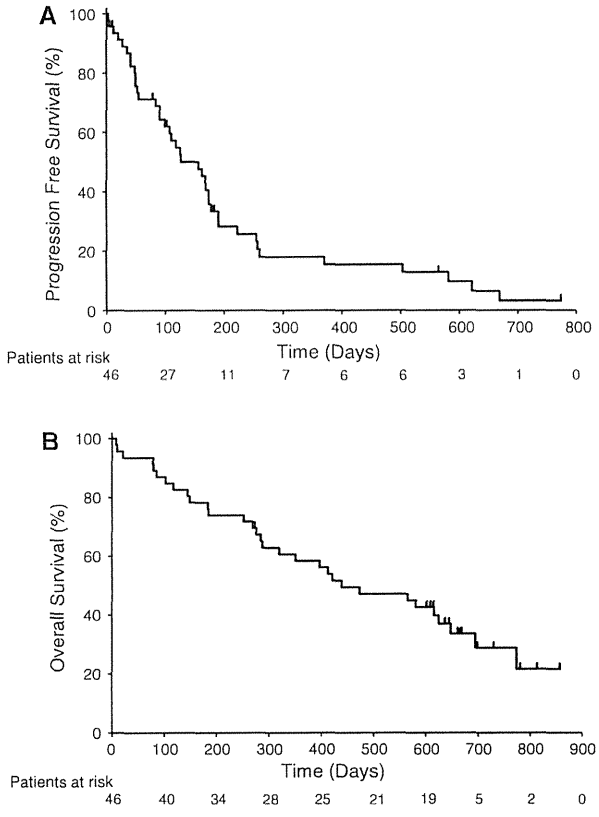

Fig. 1 **a** Kaplan–Meier curve for progression-free survival, **b** Kaplan–Meier curve for overall survival

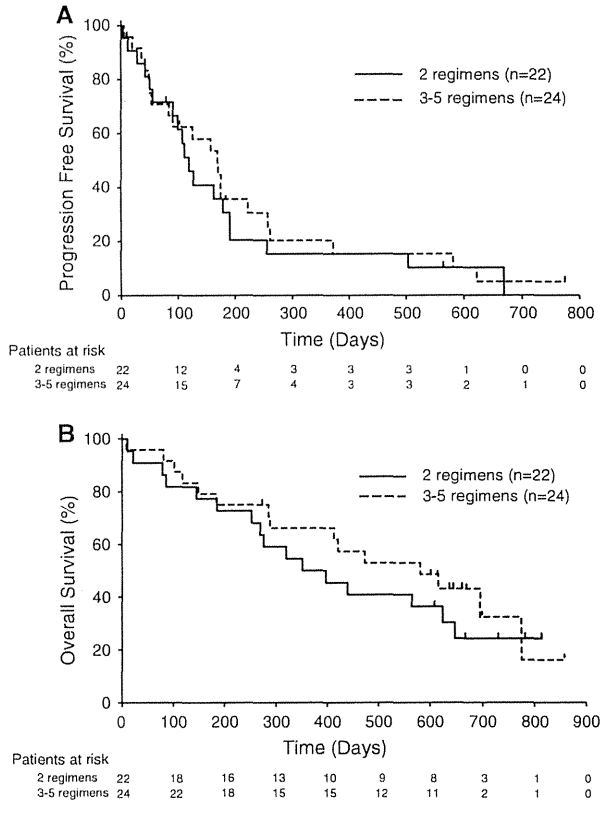

Fig. 2 **a** Kaplan–Meier curve for progression-free survival by number of prior chemotherapy regimens, **b** Kaplan–Meier curve for overall survival by number of prior chemotherapy regimens

(i.e., 8.3, 7.8, and 6.7 months, respectively). It was also virtually the same as the 14.0 months observed in the docetaxel group in the V-15-32 study. Of particular note is the 19.1-months MST among fourth- to sixth-line, which came in much better than the 12.3 months among third-line. The fact that six patients among third-line (6/22; 27.3 %) and a slightly larger number (8/24; 33.3 %) of fourth- to sixth-line were positive for the EGFR mutation and there were more (14/24; 58.3 %) females, for whom a more favorable prognosis has been reported in the past [9], fourth- to sixth-line than third-line may have lead to the difference in MST. However, EGFR mutation-positive patients were found slightly more fourth- to sixth-line compared to third-line, all patients in the fourth- to sixth-line were previously treated with EGFR-TKI, and it was just hard to explain the reason for the better MST.

The RR was 8.7 %. It was 9.1 % in the pemetrexed group in the JMEI study, 5.8 % from the docetaxel group in the TAX320 study rate, and 8.9 % in the erlotinib group in the BR.21 study. Accordingly, the RR in our study was comparable to all of these studies. Our study also showed somewhat better DCR (63.0 %) than in the other above-mentioned studies.

In regard to the hematological toxicity, there were 11 patients with grade 3/4 neutropenia but only 2 required G-CSF. Moreover, none of the grade 3 or 4 anemia or thrombocytopenia required transfusion. These findings suggested that bone marrow suppression due to pemetrexed could be managed even among patients with a relatively large number of previous treatment regimens. In regard to the non-hematological toxicity, 3 patients presented grade 4 dyspnea which due to worsening of the original disease. While grade 3 or 4 AST elevation, creatinine elevation, hyponatremia, hyperkalemia, hypercalcemia, and systemic malaise were observed, no febrile neutropenia or grade 3 or above interstitial pneumonia was observed. There was no treatment-related death, either. These findings suggested safety issues with pemetrexed therapy in the target group in this study.

Despite the RR of 8.7 % not being very favorable, the PFS of 5.2 months and OS of 14.4 months were favorable. Chang et al. [10] conducted retrospective analysis of 110 patients who underwent third- or fourth-line pemetrexed. It showed a PFS of 3.2 months and OS of 11.6 months. Moreover, Asahina et al. [11] also conducted retrospective

Table 2 Tumor response in evaluable patients according to RECIST

	All lines ($n = 46$)	Third line ($n = 22$)	Fourth–sixth lines ($n = 24$)
Complete response, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response, *n* (%)	4 (8.7)	1 (4.5)	3 (12.5)
Stable disease, *n* (%)	25 (54.3)	12 (54.6)	13 (54.2)
Progressive disease, *n* (%)	13 (28.3)	5 (22.7)	8 (33.3)
Not evaluable, *n* (%)	4 (8.7)	4 (18.2)	0 (0.0)
Response rate (%)	8.7	4.5	12.5
95 % CI (%)	0.6–16.8	0.0–13.2	0.0–25.7
Disease control rate (%)	63.0	59.1	66.7
95 % CI (%)	49.1–75.5	38.5–79.6	47.8–85.5

Table 3 Maximum toxicity grades associated with chemotherapy

	All lines (n=46)			Third line (n=22)			Fourth–sixth lines (n=24)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hematologic toxicity, n (%)									
Leukopenia	31 (67)	8 (17)	0 (0)	10 (45)	5 (23)	0 (0)	17 (71)	3 (13)	0 (0)
Neutropenia	35 (76)	6 (13)	5 (11)	18 (82)	4 (18)	3 (14)	17 (71)	2 (8)	2 (8)
Anemia	37 (80)	4 (9)	1 (2)	18 (82)	2 (9)	1 (5)	19 (79)	2 (8)	0 (0)
Thrombocytopenia	21 (46)	1 (2)	1 (2)	10 (45)	0 (0)	1 (5)	11 (46)	1 (4)	0 (0)
Febrile neutropenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Non-hematologic toxicity, n (%)									
Aspartate aminotransferase increased	26 (57)	0 (0)	1 (2)	11 (50)	0 (0)	1 (5)	15 (63)	0 (0)	0 (0)
Alanine transaminase increased	29 (63)	2 (4)	1 (2)	14 (64)	0 (0)	1 (5)	15 (63)	2 (8)	0 (0)
Creatinine increased	6 (13)	0 (0)	1 (2)	1 (5)	0 (0)	0 (0)	5 (21)	0 (0)	1 (4)
Hyponatremia	9 (20)	1 (2)	0 (0)	6 (27)	1 (5)	0 (0)	3 (13)	0 (0)	0 (0)
Hyperkalemia	16 (35)	2 (4)	1 (2)	10 (45)	0 (0)	1 (5)	6 (25)	2 (8)	0 (0)
Hypercalcemia	4 (9)	0 (0)	1 (2)	3 (14)	0 (0)	0 (0)	1 (4)	0 (0)	1 (4)
Fatigue	34 (74)	2 (4)	1 (2)	14 (64)	1 (5)	0 (0)	20 (83)	1 (4)	1 (4)
Nausea	18 (39)	1 (2)	0 (0)	9 (41)	0 (0)	0 (0)	9 (38)	1 (4)	0 (0)
Vomiting	12 (26)	1 (2)	0 (0)	6 (27)	0 (0)	0 (0)	6 (25)	1 (4)	0 (0)
Constipation	10 (22)	0 (0)	0 (0)	3 (14)	0 (0)	0 (0)	7 (29)	0 (0)	0 (0)
Rash	12 (26)	0 (0)	0 (0)	7 (32)	0 (0)	0 (0)	5 (21)	0 (0)	0 (0)
Mucositis/stomatitis	2 (4)	1 (2)	0 (0)	2 (9)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Sensory neuropathy	7 (15)	0 (0)	0 (0)	2 (9)	0 (0)	0 (0)	5 (21)	0 (0)	0 (0)
Motor neuropathy	2 (4)	1 (2)	0 (0)	1 (5)	0 (0)	0 (0)	1 (4)	1 (4)	0 (0)
Dizziness	3 (7)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	3 (13)	2 (8)	0 (0)
Dyspnea	10 (22)	0 (0)	3 (7)	6 (27)	0 (0)	2 (9)	4 (17)	0 (0)	1 (4)
Infection	3 (7)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	2 (8)	0 (0)	0 (0)
Interstitial pneumonia	1 (2)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastric hemorrhage	1 (2)	1 (2)	0 (0)	1 (5)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)

analysis on third- and fourth-line chemotherapy. They reported relatively favorable findings, i.e., third-line OS of 12 months fourth-line of 9.9 months. Considering that none of these reports mentioned very much worsening in OS even among heavily treated patients, the selection of a regimen with feasible toxicity that can be taken for a long term, such as pemetrexed, for heavily treated patients with maintained PS (e.g., the target patients in our study) may contribute to survival. And, we anticipate seeing comparative studies within further examination of these types of targets.

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Conflict of interest The authors have no conflict of interest to declare.

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ORIGINAL REPORT

Phase III Study Comparing Amrubicin Plus Cisplatin With Irinotecan Plus Cisplatin in the Treatment of Extensive-Disease Small-Cell Lung Cancer: JCOG 0509

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Clinical trial information: UMIN000000720 (registered at University Hospital Medical Information Network Clinical Trials Registry).

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ABSTRACT

Purpose
This randomized phase III trial was conducted to confirm noninferiority of amrubicin plus cisplatin (AP) compared with irinotecan plus cisplatin (IP) in terms of overall survival (OS) in chemotherapy-naive patients with extensive-disease (ED) small-cell lung cancer (SCLC).

Patients and Methods
Chemotherapy-naive patients with ED-SCLC were randomly assigned to receive IP, composed of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 every 4 weeks, or AP, composed of amrubicin 40 mg/m^2 on days 1, 2, and 3 and cisplatin 60 mg/m^2 on day 1 every 3 weeks.

Results
A total of 284 patients were randomly assigned to IP (n = 142) and AP (n = 142) arms. The point estimate of OS hazard ratio (HR) for AP to IP in the second interim analysis exceeded the noninferior margin (HR, 1.31), resulting in early publication because of futility. In updated analysis, median survival time was 17.7 (IP) versus 15.0 months (AP; HR, 1.43; 95% CI, 1.10 to 1.85), median progression-free survival was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.16 to 1.73), and response rate was 72.3% (IP) versus 77.9% (AP; $P = .33$). Adverse events observed in IP and AP arms were grade 4 neutropenia (22.5% *v* 79.3%), grade 3 to 4 febrile neutropenia (10.6% *v* 32.1%), and grade 3 to 4 diarrhea (7.7% *v* 1.4%).

Conclusion
AP proved inferior to IP in this trial, perhaps because the efficacy of amrubicin as a salvage therapy was differentially beneficial to IP. IP remains the standard treatment for extensive-stage SCLC in Japan.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide,[1] and small-cell lung cancer (SCLC) accounts for almost 13% of all new cases.[2] More than half of these patients are diagnosed with extensive-disease (ED) SCLC.[3] SCLC refers to a rapidly proliferating tumor that is highly sensitive to chemotherapy. However, rapid emergence of clinical drug resistance has resulted in poor prognosis, with almost all such patients dead within 2 years of initial diagnosis.[3] Thus, there is a need for new and effective therapeutic options for ED-SCLC.

The combination of etoposide and cisplatin (EP) has been standard treatment for ED-SCLC for decades. In 2002, a phase III trial conducted by the Japan Clinical Oncology Group (JCOG 9511) demonstrated the superiority of irinotecan plus cisplatin (IP) over EP for patients with ED-SCLC.[4] Median survival time (MST) and 1-year survival for the IP and EP arms were 12.8 versus 9.4 months and 58.4% versus 37.7%, respectively, but patients in the IP arm experienced a significantly higher proportion of grade 3 to 4 diarrhea. Although two randomized phase III trials have failed to confirm the superiority of IP over EP for chemotherapy-naive patients with SCLC in North America and Australia,[5-7] IP is considered equivalent to EP and one of the standard ED-SCLC regimens in Japan.

Amrubicin is a completely synthetic anthracycline derivative that is converted to an active metabolite, amrubicinol, and it is a potent topoisomerase

II inhibitor.[7] The high degree of therapeutic activity of amrubicin is caused by the selective distribution of amrubicinol, which is 10× to 100× more cytotoxic than its parent compound, amrubicin.[8,9]

A phase II study of amrubicin as single-agent therapy for previously untreated ED-SCLC yielded a response rate (RR) of 76%, complete response (CR) rate of 9%, and MST of 11.7 months,[10] similar to outcomes for platinum-based doublets at the time. Moreover, a phase I/II study of amrubicin plus cisplatin (AP) recommended administration of amrubicin 40 mg/m^2 on days 1, 2, and 3 with cisplatin 60 mg/m^2 on day 1 every 3 weeks. An RR of 87.8% and MST of 13.6 months were demonstrated in the patients treated with the recommended dose.[11] The major toxicity of the AP regimen was hematologic, which was acceptable because of the absence of febrile neutropenia (FN). Moreover, the incidence of grade 3 to 4 diarrhea, a concern with IP, was only 4.9%. Therefore, we believed AP might be a new effective treatment option for ED-SCLC, with a more favorable toxicity profile than IP. We undertook a multicenter, randomized, phase III noninferiority trial of AP compared with IP in previously untreated patients with ED-SCLC.

PATIENTS AND METHODS

Patient Selection

Patients were considered eligible if they met the following criteria: histologically or cytologically demonstrated ED-stage SCLC (defined as ≥ one of following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion, pericardial effusion), chemotherapy naive, age 20 to 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to1, no prior chemotherapy or radiotherapy for any cancers, and adequate organ function, defined as leukocyte count ≥ 4,000/mm^3, hemoglobin ≥ 9.0 g/dL, platelet count ≥ 100,000/mm^3, total bilirubin ≤ 2.0 mg/dL, AST ≤ 100 IU/L, ALT ≤ 100 IU/L, serum creatinine ≤ 1.5 mg/dL, and partial pressure of arterial blood gas without oxygen inhalation ≥ 70 torr. Patients had normal ECG and were asked to respond to a quality-of-life (QOL) questionnaire before enrollment. Patients were excluded if they had other unrelated invasive malignancies requiring ongoing therapy, serious tumor-related complication, active bacterial or fungal infection, diarrhea, intestinal paralysis or obstruction, evidence of interstitial pneumonia or pulmonary fibrosis on chest x-ray, received or expected to receive long-term treatment (≥ 50 days) with nonsteroidal anti-inflammatory drugs or steroids, serious cardiac disease, serious psychiatric disorder, pregnancy, active gastroduodenal ulcer, or history of myocardial infarction within 12 months. All enrolled patients provided written informed consent to participate in the study.

Treatment Plan

Patients were randomly assigned at a one-to-one ratio to receive either AP or IP. Random assignment was adjusted according to the following stratification factors: ECOG PS, institution, and sex. The IP regimen consisted of four cycles of irinotecan 60 mg/m^2 intravenously (IV) on days 1, 8, and 15 and cisplatin 60 mg/m^2 IV on day 1. Cycle length for this arm was 4 weeks. The AP regimen initially consisted of four cycles of amrubicin 40 mg/m^2 IV on days 1, 2, and 3 and cisplatin 60 mg/m^2 IV on day 1 every 3 weeks. However, because of the high incidence of severe hematologic toxicities, the protocol was revised to reduce the initial dose of amrubicin to 35 mg/m^2 in the AP group after 66% of patients (94 of 142) in the AP arm had been enrolled. The subsequent cycles of both arms were begun if absolute leukocyte count ≥ 3,000/μL, platelet count ≥ 100,000/μL, serum creatinine ≤ 1.5 mg/dL, and treatment-related nonhematologic toxicities (excluding alopecia, weight loss, and hyponatremia) had been resolved to grade ≤ 1. In regard to dose modification, if during the previous course the patient presented with thrombocytopenia (platelet count < 20,000/mm^3) and/or grade 3 nonhematologic toxicity including FN and diarrhea, the dose of irinotecan was reduced by 10 mg/m^2 and the dose of amrubicin by 5 mg/m^2 in the next cycle. The dose of cisplatin was reduced by 20 mg/m^2 for subsequent courses in the event of any of the following toxicities: creatinine > 1.5 to ≤ 2.0 mg/dL, grade 3 nonhematologic toxicity, grade ≥ 2 neuropathy (sensory or motor), and grade ≥ 2 muscle or joint pain. Prophylactic administration of granulocyte colony-stimulating factor was not allowed in the first cycle. After the fourth cycle, initially prophylactic cranial irradiation (PCI) was conducted as per institutional policy. However, because of the report at the 2007 Annual Meeting of the American Society of Clinical Oncology stating that addition of PCI for ED-SCLC responders significantly extended survival,[12] the protocol was revised just 4 months after the start of patient enrollment so that patients with CR or tumor elimination would additionally receive PCI.

Response and Toxicity Evaluations

Baseline evaluation consisted of complete medical history and physical examination, ECG, ECOG PS, complete blood count, blood chemistry, blood gas analysis, computed tomography (CT) scan of the chest, CT or ultrasound of the abdomen, magnetic resonance imaging or CT of the brain, and bone scan or positron emission tomography. During treatment within the study, complete blood count, blood chemistry, and complete physical examination with clinical assessment were performed at least every week. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 3). Chest x-ray was performed every cycle during protocol treatment, whether or not there was evidence of progression. All responses were defined according to RECIST (version 1.0). We evaluated patient QOL twice—once at baseline and once after completion of the second course (8 weeks in IP arm, 6 weeks in AP arm after treatment initiation)—using a QOL questionnaire for patients with cancer treated with anticancer drugs (QOL-ACD) and QOL Questionnaire Core 30 (QLQ-C30; diarrhea score). The primary metric used to analyze QOL was a comparison between arms in terms of improvement of physical status score over baseline QOL questionnaire.

End Points

The objective of this randomized phase III study was to establish the noninferiority of AP compared with IP as first-line therapy in patients with ED-SCLC. The primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), RR, adverse events (AEs), grade 3 to 4 diarrhea, and QOL.

Study Design and Statistical Analysis

This trial was a multicenter randomized trial. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review board of each participating institution.

The trial was designed to achieve at least 70% power to confirm noninferiority of AP compared with IP, with a noninferiority margin of 1.31 in terms of hazard ratio (HR), MST of 12.8 months in both arms, and one-sided $\alpha = 0.05$. We believed 3 months would be the maximum allowable noninferiority margin in the case of a less-toxic regimen with a different toxicity profile—a profile that we had expected from the phase I/II study. An MST 3 months shorter than that of the IP arm would correspond to an HR of 1.31. The planned sample size was 282 patients, determined by the methods of Schoenfeld and Richter,[13] with 3 years of accrual and 3 years of follow-up. Because of an insufficient accrual rate during the study, the accrual period was revised to 4 years.

An interim analysis was scheduled because of the futility of the trial at the halfway mark of registration. The results from the interim analysis were reviewed by the JCOG Data and Safety Monitoring Committee, and investigators were blinded for the results. After the first interim analysis, the protocol was revised to add second interim analysis after all patients had been registered. Multiplicity for the primary end point was adjusted using O'Brien-Fleming–type alpha spending function.[14] The primary end point—OS—was analyzed using stratified Cox regression analysis with PS (0 *v* 1) and sex (male *v* female) as strata for all eligible patients. Except for the primary analysis, OS and PFS were analyzed using unstratified Cox regression analysis. OS and PFS were estimated using the Kaplan-Meier method. RRs were compared using Fisher's exact test. QOL scores were analyzed using logistic regression with covariate, treatment arm, and QOL scores at baseline. All *P* values are two sided, except for the primary analysis of the noninferiority hypothesis. Statistical analyses were conducted using SAS software (version 9.1 or 9.2; SAS Institute, Cary, NC).

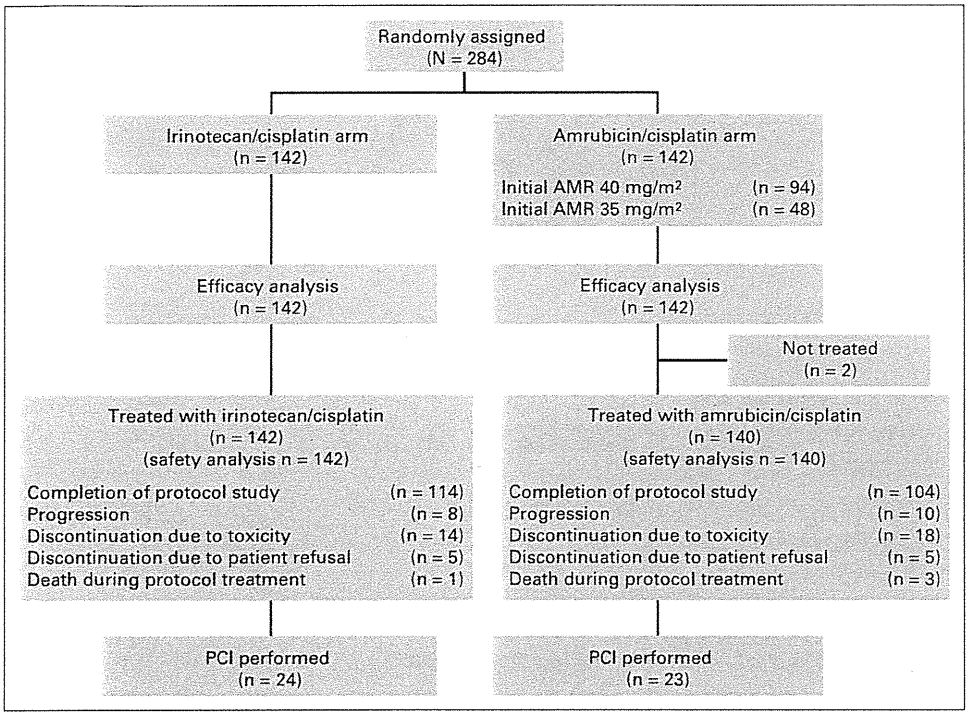

Fig 1. CONSORT diagram. AMR, amrubicin; PCI, prophylactic cranial irradiation.

RESULTS

From May 2007 to December 2010, 284 patients from 35 institutions were enrolled onto the study. All patients were deemed eligible; 142 patients were randomly assigned to the IP arm and 142 to the AP arm (Fig 1). Baseline characteristics were well balanced between the arms (Table 1). All 284 patients were included in the analysis for OS, PFS, and response. Patients who received at least one cycle of study treatment (n = 282) were assessable for toxicity analysis.

Treatment Delivery

Table 2 lists the number of cycles delivered. There were no significant differences between the two arms in treatment delivery. Two patients in the AP arm did not receive any protocol treatment. For the remaining 142 and 140 patients, the proportions receiving the planned four cycles of chemotherapy were 81% and 73.2% in the IP and AP arms, respectively. In the AP arm, 67% (63 of 94) of those who received an initial dose of 40 mg/m^2 completed four cycles, whereas in the AP arm, 85.4% of those who received 35 mg/m^2 completed four cycles; 4.9% (seven of 142) in the IP group and 7% (10 of 142) in the AP group received < two thirds of the planned dose of cisplatin. The interruption rates before protocol completion in the IP and AP arms were 19.7% and 26.8%, respectively; 13.4% and 16.2% of the patients in the IP and AP arms, respectively, had their treatment interrupted because of toxicity. In the IP and AP arms, 24 and 23 patients underwent PCI, respectively.

Toxicity

Table 3 lists grade ≥ 3 major toxicities. The most common grade ≥ 3 AEs in the AP arm were myelosuppression and FN. Diarrhea represented the predominant type of grade ≥ 3 toxicity in the IP arm. Myelosuppression was improved by reducing the initial dose of amrubicin: grade 3 to 4 leukopenia (from 77.2% to 62.5%), neutropenia (from 96.7% to 93.8%), anemia (from 43.5% to 22.9%), thrombocytopenia (from 35.9% to 10.4%), and FN (from 37% to 22.9%).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	IP Arm (n = 142) No.	IP Arm (n = 142) %	AP Arm (n = 142) No.	AP Arm (n = 142) %
Sex				
Male	120	84.5	119	83.8
Female	22	15.5	23	16.2
Age, years				
Median	63		63	
Range	39-70		29-70	
ECOG PS				
0	78	54.9	80	56.3
1	64	45.1	62	43.7
Measurable lesions				
None	1	0.7	2	1.4
Yes	141	99.3	140	98.6
Smoking status				
Nonsmoker	3	2.1	3	2.1
Smoker	139	97.9	139	97.9
Metastasis (overlapped)				
Lung	9	6.3	14	9.9
Bone	25	17.6	31	21.8
Brain	32	22.5	41	28.9
Liver	35	24.6	45	31.7
Others	68	47.9	64	45.1

Abbreviations: AP, amrubicin plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; IP, irinotecan plus cisplatin.

Table 2. Delivered Cycles

No. of Cycles	IP Arm (n = 142) No.	IP Arm (n = 142) %	AP Arm (n = 142) No.	AP Arm (n = 142) %
0	0	0.0	2	1.4
1	7	4.9	8	5.6
2	10	7.0	14	9.9
3	10	7.0	14	9.9
4	115	81.0	104	73.2

Abbreviations: AP, amrubicin plus cisplatin; IP, irinotecan plus cisplatin.

One treatment-related death occurred in the IP arm (resulting from infection), and two occurred in the AP arm (one resulting from infection, and other resulting from pulmonary hemorrhage).

Efficacy

In the first interim analysis, the HR was 1.25 (99.9% CI, 0.28 to 5.59; information time, 0.16). The second interim analysis was conducted after completion of patient accrual based on the data as of May 2011. It showed that the median OS for AP (15.0 months) was much worse than that for IP (18.3 months) and that the HR was 1.41 (96.3% CI, 1.03 to 1.93) in stratified Cox regression. The point estimate of HR in OS for AP to IP exceeded the noninferiority margin (HR, 1.31); therefore, the Data Safety Monitoring Committee recommended early publication because of futility according to the preplanned decision rule that a point estimate of HR of AP to IP exceed the noninferiority margin (HR > 1.31). The Bayesian predictive probability that noninferiority would be shown with statistical significance at the end of this trial was 16.2%. Median PFS was 5.7 (IP) versus 5.2 months (AP; HR, 1.43; 95% CI, 1.13 to 1.82). RR was 72.3% (IP) versus 77.9% (AP; $P = .33$). Even updated analysis, as of May 2012, showed OS to be inferior in the AP arm (17.7 *v* 15.0 months; HR, 1.43; 95% CI, 1.10 to 1.85; Fig 2A). Median PFS was 5.6 (IP) versus 5.1 months (AP; HR, 1.42; 95% CI, 1.12 to 1.80; Fig 2B). The initial dose reduction in amrubicin had no impact on any efficacy results when the dose was reduced to 35 mg (Table 4).

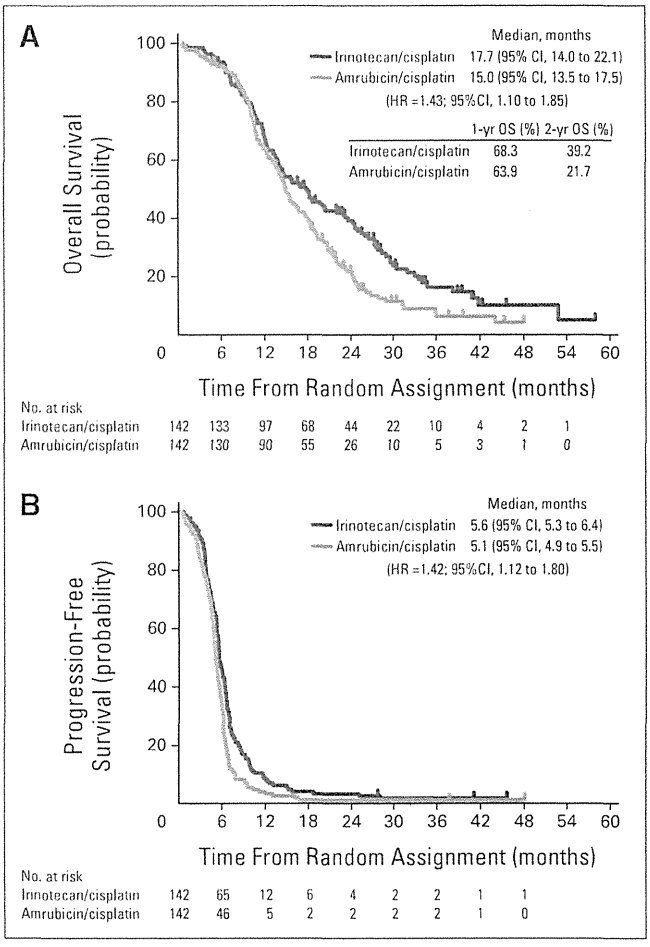

Fig 2. (A) Overall and (B) progression-free survival for intent-to-treat population (n = 284). HR, hazard ratio.

Table 3. Toxicities

Toxicity	Regimen by Grade (%) IP Arm (n = 142)* All	3	4	AP Arm (n = 140)† All	3	4
Hematologic						
Leukopenia	88.7	20.4	2.1	98.6	46.4	25.7
Neutropenia	95.8	35.9	22.5	99.3	16.4	79.3
Anemia	85.9	16.9	6.3	91.4	23.6	12.9
Thrombocytopenia	12.0	1.4	0.7	59.3	15.7	11.4
Nonhematologic						
FN	10.6	9.9	0.7	32.1	31.4	0.7
Fatigue	61.3	3.5	0.7	64.3	3.6	0.0
Nausea	78.9	6.3	0.0	79.3	4.3	0.0
Vomiting	37.3	3.5	0.0	34.3	2.1	0.0
Diarrhea	63.4	7.7	0.0	26.4	1.4	0.0
Hyponatremia	74.6	14.8	4.9	79.3	15.7	6.4
Cardiovascular events	0.0	0.0	0.0	0.0	0.0	0.0

Abbreviations: AP, amrubicin plus cisplatin; FN, febrile neutropenia; IP, irinotecan plus cisplatin.
*One treatment-related death (0.7%).
†Two treatment-related deaths (1.4%).

The QOL questionnaire was completed in most cases: 282 of 284 patients at baseline and 272 patients at the end of the second course. The proportion of improvement in physical status in terms of QOL—the primary metric used to analyze QOL—was 37.1% in the IP arm versus 31.7% in the AP arm (odds ratio, 0.72; 95% CI, 0.43 to 1.22; $P = .23$). There was no significant difference in QOL improvement.

Poststudy Treatment

Table 5 summarizes poststudy treatment. Overall, 93.7% of IP-arm patients and 92.1% of AP-arm patients received additional therapy; 89.4% of patients in the IP arm and 87.1% of those in the AP arm received second-line chemotherapy, whereas 59.2% of those in the IP arm and 62.1% of those in the AP arm received third-line chemotherapy, indicating no substantial difference in the percentage receiving poststudy treatment. Nonetheless, 61 and 34 patients in the IP arm were administered single-agent amrubicin in their second- or third-line therapy, respectively. These figures are higher than those observed in the AP arm.