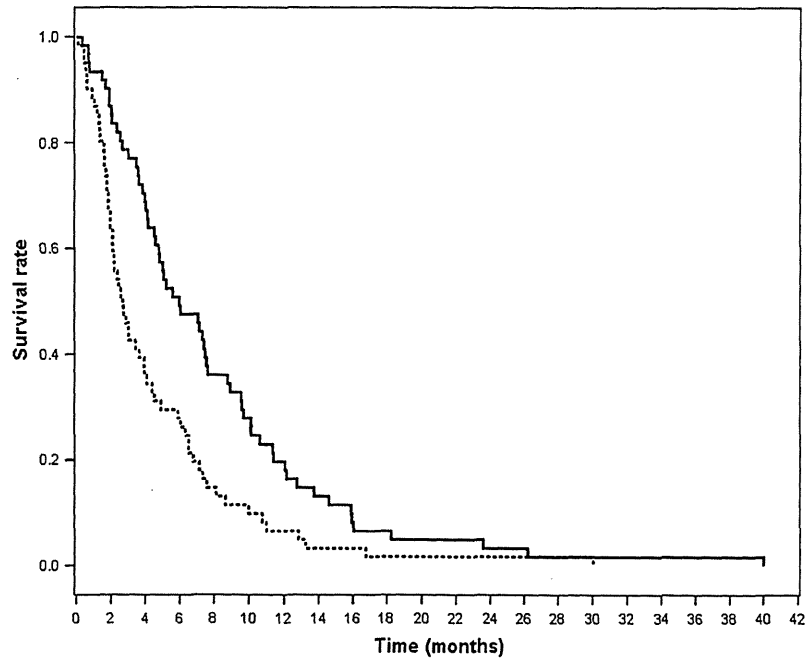

Fig. 1 Kaplan–Meier curves for overall survival (*black line*) and progression-free survival (*dotted line*). Median progression-free survival and overall survival were 2.7 months (95 % CI 1.9–3.5) and 6.0 months (95 % CI 3.6–8.4), respectively

Predictive factors

The relationships between clinical factors and the attainment of partial response to FGS were evaluated. ECOG PS >0 ($p = 0.103$), site of primary lesion($p = 0.588$), number of prior chemotherapy regimens ($p = 0.607$), history of S-1 administration ($p = 0.162$), time to treatment failure of prior treatment ($p = 0.548$), the presence of liver metastasis ($p = 0.346$), the presence of lung metastasis ($p = 0.281$), the presence of ascites ($p = 0.608$), CEA level >10 ng/ml ($p = 0.452$), CA19-9 level >2,000 IU/ml ($p = 0.588$), ALP > 500 IU/ml ($p = 0.128$), ALB < 3.5 g/dl ($p = 0.136$), CRP level $\geq$1.0 g/dl ($p = 0.281$), and a high mGPS ($p = 0.153$) were not significantly associated with response to FGS. There were no variables with p values <0.1 selected for multivariate analysis.

Discussion

This retrospective study of FGS in patients with GEM-refractory PC demonstrated an ORR of 13 %, DCR of 49 %, and median PFS and OS of 2.7 and 6.0 months, respectively. FGS showed efficacy in both S-1-naïve and non-naïve patients in this study. We explored the independent variables associated with survival in a salvage chemotherapy setting for advanced PC. This study demonstrated that the inflammation-based prognostic score (mGPS) was independently associated with survival in patients with GEM-refractory advanced PC receiving salvage chemotherapy.

In regard to treatment for GEM-refractory PC, the results of a randomized trial comparing best supportive care (BSC) versus oxaliplatin, fluorouracil, and folinic acid (OFF) indicated the benefit of second-line chemotherapy as compared to BSC alone for patients with GEM-refractory advanced pancreatic cancer. Median second-line survival time was 4.8 months for OFF treatment and 2.3 months for BSC alone [12]. However, since the patient number was small ($n = 46$), OFF has not been recognized as standard salvage chemotherapy in patients with advanced pancreatic cancer. Thus, no standard salvage chemotherapy has been established. Several clinical trials (mainly phase II) of oral fluoropyrimidine monotherapy such as S-1 have been conducted in patients with advanced PC after failure of first-line GEM or a GEM-based combination regimen [6, 13–16]. Median PFS time and median OS time of oral fluoropyrimidine monotherapy were 2.1–4.1 and 4.5–7.6 months (Table 5), which are almost the same as the results of a previous prospective study of FGS [7]. As FOLFIRINOX regimen demonstrated survival benefit over GEM in first-line setting, it could be promising salvage chemotherapy for GEM-refractory patients. Although there is no prospective study using FOLFIRINOX in second-line setting. A retrospective analysis of 27 patients with GEM-refractory PC showed median time to progression of 5.4 months, and median OS was 8.5 months [17]. Another retrospective from Korea assessed 18 patients with GEM-refractory PC noted progression-free survival of 2.8 months and overall survival of 8.4 months [18]. These results suggest the modest clinical activity regarding efficacy with the

Table 3 Univariate analysis of prognostic factors for FGS-treated patients

	n	Median survival (months)	*p* value
ECOG performance status			
0	22	9.6	0.006
1, 2	39	4.2	
Primary tumor			
Head	29	7.4	0.562
Body/tail	32	5.1	
Prior chemotherapy			
First Line	44	6.1	0.911
Second Line	17	5.2	
History of S-1 administration (including GS therapy)			
Yes	29	5.1	0.842
No	32	7.1	
TTF of prior treatment (months)			
≦6	28	5.0	0.506
>6	33	7.4	
Liver metastasis			
Present	38	4.6	0.095
Absent	23	9.6	
Lung metastasis			
Present	17	5.1	0.490
Absent	44	7.1	
Ascites			
Present	22	3.9	0.021
Absent	39	7.5	
CEA (ng/ml)			
≦10	33	9.6	<0.001
>10	28	4.6	
CA19-9 (IU/ml)			
≦2,000	32	7.1	0.028
>2,000	29	4.8	
ALP (IU/l)			
≦500	48	7.4	<0.001
>500	13	2.7	
Alb (g/dl)			
<3.5	22	3.6	<0.001
≧3.5	39	7.6	
CRP (mg/dl)			
<1.0	44	7.6	<0.001
≧1.0	17	2.4	
mGPS			
Low (0, 1)	49	7.5	<0.001
High (2)	12	2.0	

ECOG, Eastern Cooperative Oncology Group; GS, gemcitabine and S-1 combination therapy; TTF, time to treatment failure; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ALP, alkaline phosphatase; Alb, albumin; CRP, C-reactive protein; mGPS, modified Glasgow prognostic scale

Table 4 Multivariate analysis of prognostic factors for FGS-treated patients

Variable	Odds ratio	95 % confidence interval	*p* value
High mGPS (2)	6.605	2.965–14.709	<0.001
CA19-9 > 2,000	2.573	1.448–4.573	0.001
ECOG performance status >0	2.192	1.192–4.031	0.012

mGPS, modified Glasgow prognostic scale; CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group

FOLFIRINOX regimen as a second-line treatment. However, FOLFIRINOX is a potentially highly toxic combination of drugs with serious side effects, and only patients with good performance status are candidates for the regimen even in the first-line setting. Significant toxicity is a concern with FOLFIRINOX in any setting. Prospective studies are needed to better define risks and to determine FOLFIRINOX in the salvage setting.

Whether gemcitabine as FDR infusion is active even after progression during treatment with standard 30-min administration of GEM was the critical clinical question examined in this study. Differentiation between the relative roles of GEM and S-1 in overcoming tumor resistance is difficult. This retrospective study included patients with a history of S-1 administration. Subgroup analysis showed that a history of S-1 administration was not a significant prognostic factor ($p = 0.842$). This might suggest that FDR infusion of gemcitabine is efficacious ever after failure of standard GEM-based regimens.

Regarding toxicity, grade 3–4 adverse events were not frequent. One death was observed after grade 3 stroke, in a patient with other risk factors, such as age of 82 years and poor performance status. Other than this event, most episodes were reversible, and treatment was generally well tolerated in this study. The median relative dose intensity of GEM and S-1 was 92.6 and 92.3 %, respectively, indicating that treatment was carried out as scheduled in most patients. The safety profile in this study suggests that FGS can be safely administered to patients with PC even in a salvage setting, at least in selected populations. Since the FGS regimen was applied in a practical setting in this study, physical examination and laboratory tests usually were not conducted on day 8. The biweekly schedule allows enough time for recovery from myelosuppression and non-hematologic toxicity before the following cycle, enabling patients to receive treatment as scheduled.

Subgroup analysis of this study showed that high mGPS, high CA19-9 level, and poor PS were independently associated with a poor outcome. Previous reports indicated that

Table 5 Comparison between current study and previous studies on oral fluoropyrimidine-based therapy as salvage chemotherapy for advanced pancreatic cancer

Study	Phase	Regimen	*n*	ORR (%)	Median PFS (months)	Median OS (months)
Morizane et al. [6]	II	S-1	40	15	2.0	4.5
Sudo et al. [13]	II	S-1	21	9.5	4.1	6.3
Todaka et al. [14]	Retrospective	S-1	52	4	2.1	5.8
Boeck et al. [15]	II	Capecitabine	39	0	2.3	7.6
Morizane et al. [7]	II	FGS	40	18	2.8	7.0
Takahara et al. [16]	Retrospective	SOX	30	10	3.4	5.0
Current study	Retrospective	FGS	61	13.1	2.7	6.0

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; FGS, fixed dose rate infusion gemcitabine and S-1 combination therapy; SOX, S-1 and oxaliplatin combination therapy

PS, CRP, ALB, and inflammation-based prognostic score were important prognostic factors in a first-line setting [19–22]. mGPS was reported to be identified as an independent predictor of survival in patients undergoing potentially curative pancreatic resection [23]. It is now widely accepted that inflammation-based prognostic score is a reliable indicator of survival for several malignant tumors [10, 11]. Our results suggested that it is also an important prognostic factor in the setting of salvage chemotherapy for advance pancreatic cancer.

It is important to point out the limitations of this retrospective study. Patients who received FGS may have been more fit, better able to tolerate it and therefore more likely to derive benefit from it. In addition, the gap between the median OS time and the median PFS time in the present study was relatively large. In this study, 27.9 % of patients received chemotherapy after failure of FGS. Post-treatment, including paclitaxel and clinical trial drugs may prolong the survival of selected patients. Although the reason for this gap is unknown, bias arising from the selection of patients with a good general condition may explain these findings. On the other hand, this retrospective study included patients after failure of second-line chemotherapy as well as those after failure of first-line chemotherapy. It thus seems that the patient backgrounds were rather poor when compared to those in recent phase II trials [6, 7, 13, 15].

In conclusion, FGS as salvage chemotherapy in patients with GEM-refractory advanced PC might be effective and well tolerated in a practical setting. Furthermore, the FGS regimen might possibly show some benefit in patients even after both GEM and S-1 failure. These results suggest that it would be of value to further investigate FGS in a clinical trial in patients with GEM-refractory pancreatic cancer. mGPS is simple and useful as a novel predictor of survival for patients with GEM-refractory advanced PC. mGPS is helpful for planning salvage treatment for these patients.

Conflict of interest Junji Furuse receives research funding and honoraria from Taiho Pharmaceutical Co. and Eli Lilly.

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ORIGINAL REPORT

Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L

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See accompanying editorial on page 534 and article on page 567

ABSTRACT

Purpose
This phase III trial aimed to confirm the superiority of weekly docetaxel and cisplatin over docetaxel monotherapy in elderly patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Chemotherapy-naïve patients with stage III, stage IV, or recurrent NSCLC age ≥ 70 years with a performance status of 0 or 1 who were considered unsuitable for bolus cisplatin administration were randomly assigned to receive docetaxel 60 mg/m^2 on day 1, every 3 weeks, or docetaxel 20 mg/m^2 plus cisplatin 25 mg/m^2 on days 1, 8, and 15, every 4 weeks. The primary end point was overall survival (OS).

Results
In the first interim analysis, OS of the doublet arm was inferior to that of the monotherapy arm (hazard ratio [HR], 1.56; 95% CI, 0.98 to 2.49), and the predictive probability that the doublet arm would be statistically superior to the monotherapy arm on final analysis was 0.996%, which led to early study termination. In total, 276 patients with a median age of 76 years (range, 70 to 87 years) were enrolled. At the updated analysis, the median survival time was 14.8 months for the monotherapy arm and 13.3 months for the doublet arm (HR, 1.18; 95% CI, 0.83 to 1.69). The rates of grade ≥ 3 neutropenia and febrile neutropenia were higher in the monotherapy arm, and those of anorexia and hyponatremia were higher in the doublet arm.

Conclusion
This study failed to demonstrate any survival advantage of weekly docetaxel plus cisplatin over docetaxel monotherapy as first-line chemotherapy for advanced NSCLC in elderly patients.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death in most developed countries. Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and more than 50% of patients with NSCLC already have advanced disease at diagnosis.[1] The number of elderly patients with lung cancer has also increased, and the median age at diagnosis is 70 years.[2]

The Elderly Lung Cancer Vinorelbine Italian Study, in which single-agent vinorelbine was compared with the best supportive care, first demonstrated the benefits of chemotherapy in elderly patients with advanced NSCLC.[3] In the Multicenter Italian Lung Cancer in the Elderly Study, a combination of vinorelbine plus gemcitabine did not improve survival over vinorelbine or gemcitabine alone and only increased the toxicity frequency.[4] Therefore, single-agent vinorelbine or gemcitabine was established as the standard treatment for elderly patients with NSCLC. We compared docetaxel (every 3 weeks) with vinorelbine in the West Japan Thoracic Oncology Group (the former name of the West Japan Oncology Group [WJOG]) 9904 study, which revealed significantly superior responses and better survival in the docetaxel arm.[5]

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However, platinum-doublet chemotherapy has been recommended for patients with NSCLC with a performance status (PS) of 0 or 1,[6-8] and several retrospective subgroup analyses of large phase III trials have shown that the efficacy of platinum-doublet chemotherapy is similar in selected elderly patients and younger patients.[9,10] However, drug excretion or metabolic abilities generally decline because of age-related insufficiencies, especially in renal function. Therefore, modifications of anticancer drug dosages or schedules are recommended in chemotherapy for elderly patients with cancer.[11] In Japan, phase I[12] and II trials of weekly docetaxel plus cisplatin (DP) were conducted in elderly patients with NSCLC. The phase II study revealed a response rate (RR) of 52% (95% CI, 31% to 67%), a median survival time of 15.8 months, and no grade 4 toxicity.[13] On the basis of these promising results, we conducted a randomized phase III trial, the Japan Clinical Oncology Group (JCOG) 0207 trial, to compare DP with single-agent docetaxel. For the control arm, we chose weekly split docetaxel to investigate the effects of added cisplatin. In the second interim analysis, the overall survival (OS) seemed to be more favorable in the DP arm; however, an unexpected large difference was observed in the subgroup of patients age less than 75 years.[14] Therefore, considering the potential disadvantage of single-agent docetaxel therapy in this subgroup, we terminated the study and designed a new phase III trial in which the control arm received bolus infusions of docetaxel every 3 weeks, based on the West Japan Thoracic Oncology Group 9904 study.[5]

PATIENTS AND METHODS

Patients

Patients eligible for this study included chemotherapy-naïve patients with histologically or cytologically confirmed stage III (no indication for definitive radiotherapy), stage IV, or recurrent NSCLC who were age ≥ 70 years, with an Eastern Cooperative Oncology Group PS of 0 or 1 and adequate organ functioning, but who were unsuitable for bolus cisplatin administration. Considering that the age group of 70 to 74 years included those who were suitable and unsuitable for bolus cisplatin administration, we classified the reasons for administration unsuitability in this age group into six categories and examined patients for these conditions before enrollment. The pre-enrollment evaluation is described in the Appendix and Appendix Table A1 (online only). Prior radiotherapy, except for the primary lesion, was permitted if it had been completed at least 2 weeks before enrollment onto the study. Patients with symptomatic brain metastasis, active malignancy within the previous 5 years, superior vena cava syndrome, massive pleural effusion or ascites, critical vertebral metastasis, uncontrolled hypertension or diabetes, severe heart disease, active infection, hepatitis virus B surface antigen seropositivity, pulmonary fibrosis, polysorbate 80 hypersensitivity, or steroid dependence were excluded.

The study protocol was reviewed and approved by the JCOG Protocol Review Committee, WJOG executive board, and institutional review boards of each participating institution before study initiation. All patients provided written informed consent before enrollment.

Study Design and Treatment Plan

Eligible patients were randomly assigned to either the docetaxel arm (docetaxel 60 mg/m^2 infused over 60 minutes on day 1 every 3 weeks) or the DP arm (docetaxel 20 mg/m^2 infused over 60 minutes plus cisplatin 25 mg/m^2 infused over 15 to 20 minutes on days 1, 8, and 15 every 4 weeks). Patients were randomly assigned via the minimization method to balance the arms with the institution, disease stage (III *v* IV or recurrence), and age (≥ *v* < 75 years). In the DP arm, treatment was skipped under the following conditions: total leukocyte count less than 2,000/μL, platelet count less than 50,000/μL, creatinine level ≥ 1.5 mg/dL, and presence of fever or grade ≥ 3 nonhematologic toxicity (except constipation, weight loss, cough, hoarseness, and hyponatremia) on day 8 or 15. In both arms, subsequent cycle treatment was administered when the patients met the following conditions: total leukocyte count ≥ 3,000/μL, absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000/μL, serum creatinine level less than 1.5 mg/dL, total bilirubin level less than 2.0 mg/dL, ALT/AST ≤ 100 IU/L, and PS 0 to 2. Administration procedures, dose reduction criteria, and methods are detailed in the Appendix. Both treatments were repeated until the detection of disease progression or appearance of unacceptable toxicity. Radiographic tumor evaluations were performed and assessed, according to RECIST (version 1.0),[15] by each investigator at least every two cycles. Laboratory examinations were performed at least once a week in both arms, and toxicity was assessed before every cycle and classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Second-line treatment was administered at the investigator's discretion; however, cross-over to the other treatment arm was not permitted.

Quality-of-Life Assessment

Quality of life (QOL) was assessed by symptom scores, using the seven items of the Lung Cancer subscale of the Functional Assessment of Cancer Therapy–Lung.[16] The patients scored themselves immediately after providing informed consent and after completing the second and third treatment cycles. The proportions of patients with improved scores between the baseline and the end of the third cycle in each arm were compared. Missing data after treatment initiation were considered as indicating no improvement. In addition, we compared least squared means of the total scores from repeated measures analysis of variance with treatment arm, time, and their interaction and the 95% CI at each time point.

Supplementary Ad Hoc Analysis

Additional data collection and ad hoc analysis were performed. Data on the active epidermal growth factor receptor (*EGFR*) mutation status (exon 19 deletion or L858R point mutation) and poststudy treatments were collected because these were considered factors that could potentially affect survival.

Statistical Analysis

OS was the primary trial end point. The secondary end points included RRs, progression-free survival (PFS), symptom scores, and toxicities. The study was designed to provide results with a statistical power of 80%, using a one-sided $\alpha = .05$ to detect a 33% increase in median survival from 10 to 13.3 months. A total of 364 patients was required, accrued over a 4-year period with a 1-year follow-up period. Assuming a 5% rate of ineligible patients and patients lost to follow-up, the study sample size was set at 380 patients. OS, PFS, and responses were assessed in all eligible patients on an intent-to-treat basis. OS and PFS, which are defined in the Appendix, were estimated using the Kaplan-Meier method and were compared using the stratified log-rank test, according to age. Hazard ratios (HRs) of the treatment effects were estimated using the Cox proportional hazards model. RRs were compared using Fisher's exact test.

Two interim analyses were planned, the first after 50% of the patients were enrolled and the second after enrollment was completed. In these interim analyses, the primary end point, OS, was evaluated after adjustment for multiple comparisons, according to the Lan and DeMets method.[17] The O'Brien-Fleming–type α spending function was used. *P* values presented for the primary analysis were one-sided, in accordance with the trial design, whereas the other analysis values were two-sided. All analyses were performed using SAS software, release 9.1 (SAS Institute, Cary, NC). This study is registered with University Hospital Medical Information Network Clinical Trials Registry (www.umin.ac.jp/ctr/; identification No.: UMIN000001424).

RESULTS

The first interim analysis was performed in September 2010 and included data from 221 patients. Information time, defined as the

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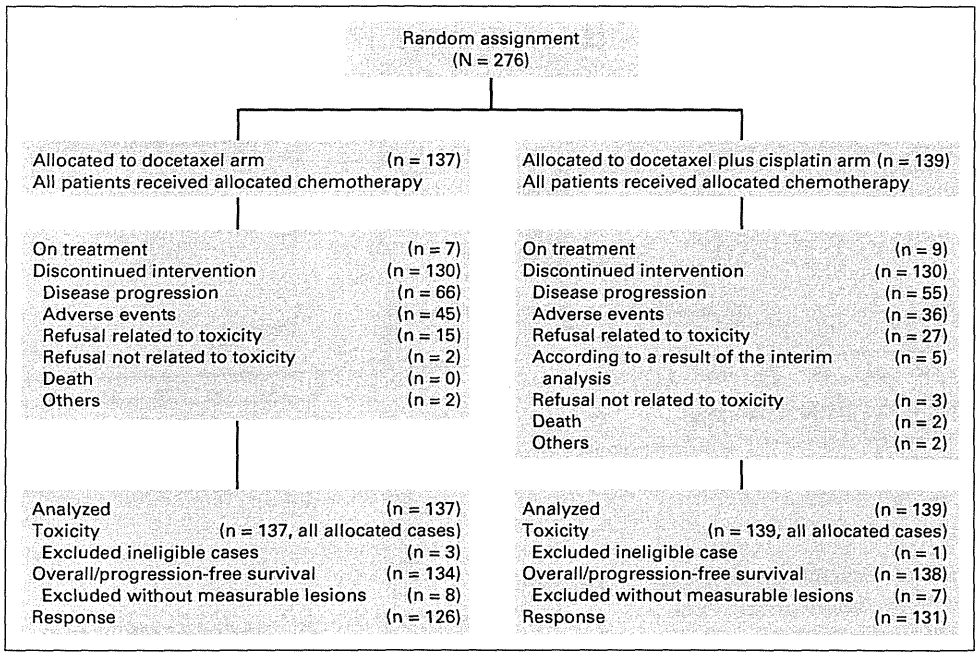

Fig 1. CONSORT diagram.

proportion of the interim events to the planned events, was 0.24 (73 of 304 events). Survival in the DP arm was inferior to that in the docetaxel arm (HR for DP to docetaxel arm, 1.56; 95% CI, 0.98 to 2.49; multiplicity-adjusted 99.99% CI, 0.62 to 3.88; one-sided $P = .97$ and two-sided $P = .06$ by stratified log-rank test), and the predictive probability that DP would be statistically superior to docetaxel on final analysis was 0.996% (< 1%). These results led to early study termination based on the recommendation of the Data and Safety Monitoring Committee, in accordance with the stopping guidelines prespecified in the protocol.

Patient Characteristics

Between October 2008 and September 2010, 276 patients (215 patients from JCOG and 61 patients from WJOG) were enrolled from 56 institutions (36 institutions affiliated with JCOG and 20 institutions affiliated with WJOG). Of these patients, 137 and 139 patients were assigned to the docetaxel and DP arms, respectively. All patients received the study treatments; therefore, all 276 patients were included in the safety analysis set. Three patients in the docetaxel arm and one patient in the DP arm were ineligible because of uncontrolled diabetes (ie, dependence on insulin injections) or previous malignancy. Therefore, these patients were excluded from survival analyses (Fig 1). Although the proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm, the patients' baseline characteristics were generally well balanced between the treatment arms (Table 1).

Treatment Delivery

The median number of treatment cycles was four (range, one to 18 cycles) in the docetaxel arm and three (range, one to six cycles) in the DP arm, and the proportion of patients in whom treatment continued for five or more cycles was higher in the docetaxel arm than in the DP arm (31% *v* 8%, respectively). In the docetaxel and DP arms, 37% and 4% of patients required one-step dose reductions, respectively. Furthermore, 19% of patients required two-step dose reductions in the docetaxel arm. In the DP arm, 19% of patients had one or more skipped treatments on day 8 or 15. The major reasons for

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Docetaxel (n = 137)		Docetaxel/Cisplatin (n = 139)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	76		76	
Range	70-87		70-86	
< 75	31	23	32	23
≥ 75	106	77	107	77
Sex				
Male	95	69	101	73
Female	42	31	38	27
Smoking status*				
Never	38	28	36	26
Smoker	98	72	101	74
ECOG PS				
0	50	36	48	35
1	87	64	91	65
Stage				
III	42	31	43	31
IV or recurrence	95	69	96	69
Histology*				
Adenocarcinoma	91	67	86	63
Squamous	32	24	39	28
Others	13	10	12	9

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
*Data for one patient in the docetaxel monotherapy arm and two patients in the docetaxel plus cisplatin arm were missing.

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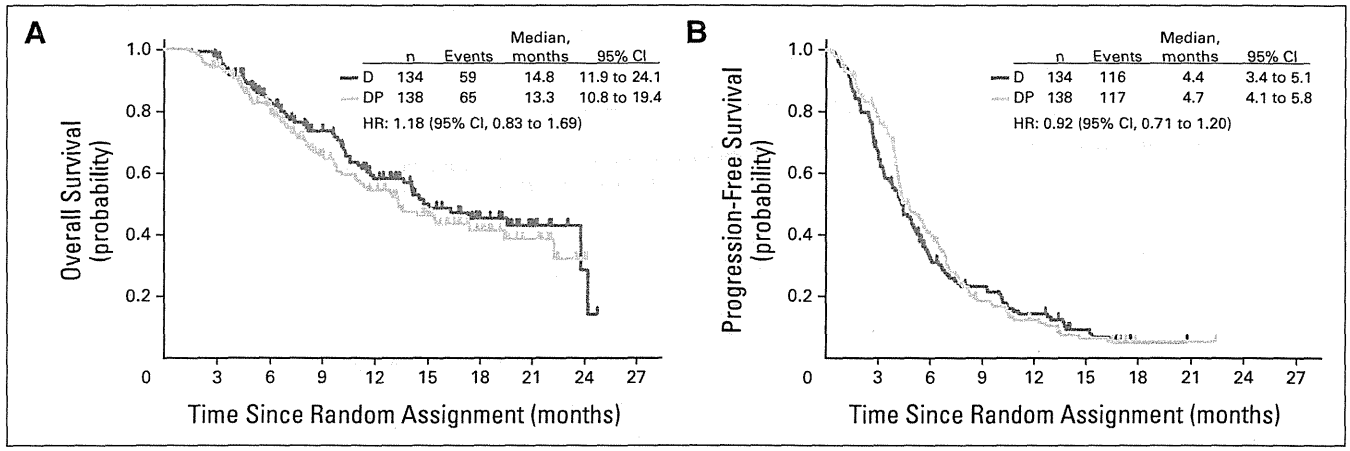

Fig 2. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival. Tick marks indicate censored patients at the data cutoff point (November 2010). D, docetaxel; DP, docetaxel plus cisplatin; HR, hazard ratio.

treatment discontinuation in the docetaxel versus DP arms were disease progression (51% *v* 42%, respectively), adverse events (35% *v* 28%, respectively), and patient refusal to continue treatment as a result of toxicity (12% *v* 21%, respectively).

Efficacy

The overall RRs were 24.6% in the docetaxel arm (95% CI, 17.4% to 33.1%) and 34.4% in the DP arm (95% CI, 26.3% to 43.2%). The difference was not statistically significant ($P = .10$).

By November 22, 2010, 124 (45.6%) of the 272 eligible patients had died (docetaxel arm, n = 59; DP arm, n = 65). The median follow-up time for all eligible patients was 9.6 months. The 1-year survival rates were 58.2% and 54.5% in the docetaxel and DP arms, respectively. The HR for OS was 1.18 (95% CI, 0.83 to 1.69; Fig 2A). The HR for PFS was 0.92 (95% CI, 0.71 to 1.20; Fig 2B).

Toxicity

Hematologic and nonhematologic toxicities are listed in Table 2. Grade ≥ 3 leukopenia and neutropenia occurred more frequently in the docetaxel arm. The incidence of grade 4 neutropenia was 67.9% in the docetaxel arm but only 0.8% in the DP arm. Febrile neutropenia was observed only in the docetaxel arm at an incidence of 15.2%. Grade ≥ 3 anemia, hyponatremia, and anorexia were observed in more than 10% of patients in the DP arm. Four treatment-related deaths occurred, all in the DP arm (2.9%), including three patients who died of pneumonitis and one patient who died of unclassified sudden death.

QOL

Symptom score questionnaire responses were collected from 271 (98.2%) of 276 patients at baseline, 258 patients (93.5%) after the second cycle, and 247 patients (89.5%) after the third cycle. The

Table 2. Toxicities

	Docetaxel (n = 137)			Docetaxel/Cisplatin (n = 139)		
Adverse Event	Grade 3 or 4 (%)	Grade 4 (%)	Missing (No.)	Grade 3 or 4 (%)	Grade 4 (%)	Missing (No.)
Hematologic*						
Leukopenia	62.7	8.2	3	5.4	0	10
Neutropenia	88.8	67.9	3	10.1	0.8	10
Anemia	3.7	0.7	3	16.3	0.8	10
Thrombocytopenia	0	0	3	0.8	0	10
Nonhematologic*						
Febrile neutropenia	15.2	0	5	0	0	8
Hyponatremia	5.2	0.7	3	14.7	0.8	10
Hypoalbuminemia	1.5	—	6	4.7	—	10
Infection	7.6	0	5	8.4	0.8	8
Anorexia	1.5	0	5	10.7	0	8
Nausea	0.8	0	5	3.8	0	8
Diarrhea	3.8	0	5	0.8	0	9
Fatigue	3.0	0	5	5.3	0	8
Pneumonitis	5.3	0	5	2.3	0.8	8

NOTE. There were four treatment-related deaths (2.9%), all in the docetaxel plus cisplatin arm, including three deaths resulting from pneumonitis and one unclassified sudden death.
*Each value was calculated while excluding patients with missing data.

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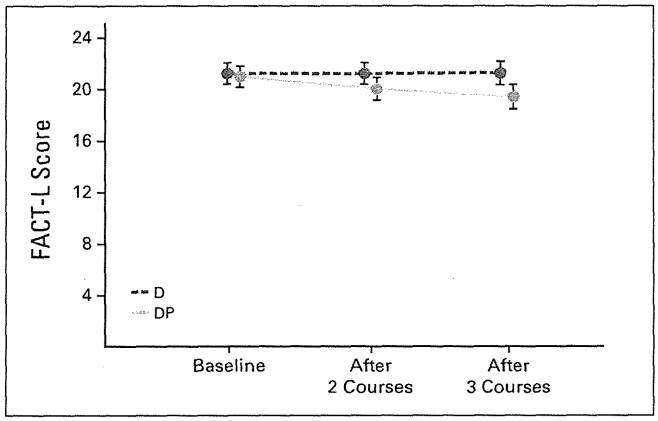

Fig 3. Quality-of-life assessments according to the seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L). Dots and error bars indicate the least squared mean total scores and 95% CI, respectively. Higher scores indicate a better quality of life. D, docetaxel; DP, docetaxel plus cisplatin.

numbers of patients with missing data because of death or severe deterioration of the patient's general condition in the docetaxel and DP arms were one and six patients, respectively, after the second cycle and six and nine patients, respectively, after the third cycle. In the docetaxel and DP arms, 39.3% (53 of 135 patients) and 36.8% (50 of 136 patients) of patients had scores that improved from baseline to the end of the third cycle, which did not constitute a significant difference. Although the mean total score remained near its baseline value in the docetaxel arm, it declined gradually in the DP arm, changing in a statistically significant manner between baseline and cycle 3 ($P < .01$; Fig 3).

Supplementary Ad Hoc Analysis

Data forms were collected from 275 patients (except one patient from the docetaxel arm). *EGFR* mutation testing was performed in 79 patients (58%) and 74 patients (53%) in the docetaxel and DP arms, respectively; the results revealed active *EGFR* mutations in 22 patients in the docetaxel arm (16% overall and 28% of those tested) and 16 patients in the DP arm (12% overall and 22% of those tested). After protocol treatment completion, further drug treatment was administered to 74 patients (54%) in the docetaxel arm and 70 patients (50%) in the DP arm. During this treatment, EGFR tyrosine kinase inhibitor was administered to 35 patients (26%) and 23 patients (17%) in the docetaxel and DP arms, respectively.

Figure 4 shows the survival HRs according to subgroup analyses of the baseline and ad hoc characteristics. No significant differences between the two treatment groups were observed in any subgroup.

DISCUSSION

The standard treatment for fit patients with advanced NSCLC is platinum-doublet chemotherapy.[6,7] Several retrospective subgroup analyses have shown that platinum-doublet chemotherapy is similarly effective in elderly and younger patients and is well tolerated despite an increased incidence of toxicity.[9,10] These retrospective analyses, however, were performed in highly selected elderly populations. Generally, elderly patients are often unsuitable candidates for bolus cisplatin administration because of comorbid illnesses and/or organ dysfunction. Therefore, we considered it important to conduct a prospective investigation to determine whether the addition of a modified platinum agent might improve survival in elderly patients with NSCLC.

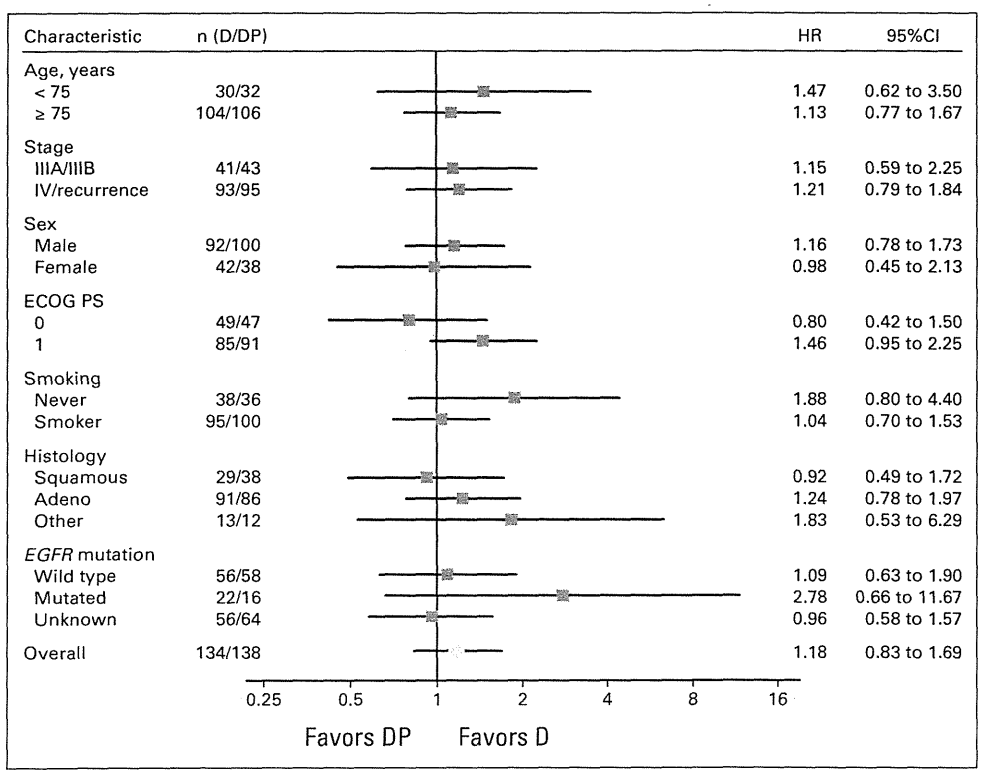

Fig 4. Subgroup analysis of overall survival. D, docetaxel; DP, docetaxel plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

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In the phase II and previous phase III trials, we demonstrated that weekly split docetaxel and additional cisplatin reduced myelotoxicity and increased RRs.[13,14] In this study, we analyzed the add-on effect of weekly cisplatin over docetaxel monotherapy. Although the DP arm tended to have higher RRs than the docetaxel arm, this was reflected in neither the PFS nor the OS.

Although we collected information on comorbid illnesses, we did not assess the Charlson comorbidity index. Comprehensive geriatric assessments, including basic activities of daily living (ADLs), instrumental ADLs, Mini-Mental State Examination, and Geriatric Depression Scale evaluation, were also conducted for exploratory purposes. Although the prognostic values of these assessments have not been validated for elderly patients with lung cancer, it was suggested that ADLs and Mini-Mental State Examination can be useful.[18] In future research, we should evaluate these factors prospectively.

The proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm. In eastern Asia, including Japan, active *EGFR* mutations are often observed in such patients and have been reported as a favorable prognostic factor in patients with NSCLC.[19,20] According to a subgroup analysis, the median survival time was 12.8 months in the 114 patients (in the docetaxel plus DP arms) without *EGFR* mutation and 24.1 months in the 38 mutation-positive patients. The proportion of patients with active *EGFR* mutations was slightly higher in the docetaxel arm than in the DP arm. However, it would have been difficult to demonstrate the superiority of the DP arm in OS, considering the slight difference in PFS, even if there were no such imbalances.

In the docetaxel arm, a higher proportion of patients required dose reductions, yet these appropriate reductions lengthened treatment. In contrast, the DP arm included fewer patients who were able to continue treatment, despite the lower proportion of dose reductions and skipped treatments. We believe that declining QOL was an important cause of treatment discontinuation in the DP arm.

The toxicity profiles also differed between the two arms. In the docetaxel arm, neutropenia was most prominent, and grade 4 neutropenia occurred in up to 68% of the patients. Consequently, febrile neutropenia was observed in 15% of the patients in the docetaxel arm, whereas no patients experienced febrile neutropenia in the DP arm. The frequency of febrile neutropenia in the docetaxel arm was similar to that seen in a previous Japanese docetaxel study for elderly patients.[5] However, because febrile neutropenia was successfully managed with appropriate supportive treatments, there were no treatment-related deaths in the docetaxel arm. However, the DP arm had higher incidences of grade ≥ 3 anemia, hyponatremia, and anorexia. We suppose that these were the main causes of the decline in the QOL score in the DP arm. The median number of treatment cycles and the proportion of patients in whom treatment could be continued for five or more cycles in the DP arm were smaller than those in the docetaxel arm. These findings could be associated with the decline in QOL and might have affected OS in the DP arm. Three of four treatment-related deaths in the DP arm were caused by pneumonitis. It was reported that weekly docetaxel administration increases the frequency of pneumonitis.[21,22] In this study, there were few differences in the frequencies of pneumonitis between the two arms; however, more severe pneumonitis was observed in the DP arm.

Quoix et al[18] demonstrated the superiority of carboplatin plus weekly paclitaxel over conventional standard therapy, namely vinorelbine or gemcitabine monotherapy, in the Intergroupe Francophone de Cancerologie Thoracique 0501 study. The usefulness of platinum-based treatments in elderly patients was first shown in a prospective study. For elderly patients with NSCLC, carboplatin combination therapy may be preferable to a split cisplatin combination. However, the high incidence of toxicity could not be ignored, because treatment-related deaths occurred in 4.4% of patients in the doublet arm but only in 1.3% of patients in the monotherapy arm.[18] In contrast, a phase I trial of combined carboplatin plus pemetrexed (PEM), followed by maintenance PEM, showed good tolerability in elderly patients with nonsquamous NSCLC.[23] We consider that the combination of carboplatin plus PEM should be compared with docetaxel monotherapy.

In conclusion, this study failed to demonstrate any advantages of weekly DP over docetaxel monotherapy as first-line chemotherapy for elderly patients with advanced NSCLC, and docetaxel every 3 weeks remains the standard treatment for elderly patients with advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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GLOSSARY TERMS

cisplatin: an inorganic platinum agent (cis-diamminedichloroplatinum) with antineoplastic activity. Cisplatin forms highly reactive, charged, platinum complexes, which bind to nucleophilic groups such as GC-rich sites in DNA, inducing intrastrand and interstrand DNA cross-links as well as DNA-protein cross-links. These cross-links result in apoptosis and cell growth inhibition. Carboplatin and oxaliplatin are other members of this class.

docetaxel: a member of the taxane group of antimitotic chemotherapy medications whose mode of action is to bind and stabilize microtubules and thus disrupt cell division.

non–small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

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Appendix

Reasons for Bolus Cisplatin Administration Unsuitability

Patients age 70 to 74 years were examined before enrollment for the following six conditions, which defined them as unsuitable for bolus cisplatin administration (Appendix Table A1): a combination of more than one mild organ dysfunction, but violating none of the inclusion criteria; a combination of comorbid illness and mild organ dysfunction, but violating none of the inclusion criteria; organ dysfunction not specified by the inclusion/exclusion criteria; a combination of more than one comorbid illness; a comorbid illness not specified by the exclusion criteria; or any other condition.

Procedures of Administration

In the docetaxel monotherapy arm, docetaxel was diluted with 250 to 500 mL of 5% glucose solution or physiologic saline and administered by intravenous infusion over 60 minutes.

In the docetaxel plus cisplatin (DP) arm, docetaxel was diluted with 250 mL of 5% glucose solution or 200 mL of physiologic saline and administered by intravenous infusion over 60 minutes. Cisplatin was administered by intravenous infusion over 15 to 20 minutes, directly or after being diluted with physiologic saline, after docetaxel administration. A total of 1,000 to 1,500 mL of fluid was administered before and after the administration of cisplatin. During treatment with cisplatin, careful attention was paid to urinary output, and diuretics such as mannitol and furosemide were administered if necessary. Antiemetics such as 5-hydroxytryptamine-3 receptor antagonists and steroids were also administered if necessary.

Dose Reduction Criteria and Methods

In both arms, the presence of grade 4 neutropenia, febrile neutropenia, or grade $\geq$ 3 nonhematologic toxicity (except anorexia, nausea, vomiting, hyponatremia, constipation, and hyperglycemia) necessitated dose reduction (docetaxel arm levels -1 and -2: docetaxel 50 and 40 mg/m^2, respectively; DP arm level -1: docetaxel 15 mg/m^2 and cisplatin 20 mg/m^2). In addition, if serum creatinine levels exceeded 2.0 mg/dL, the administration of cisplatin was stopped in subsequent cycles in the DP arm. The persistence of these toxicities after two dose-reduction steps in the docetaxel arm or one dose-reduction step of each drug in the DP arm prompted treatment discontinuation.

Definition of Overall and Progression-Free Survival

Overall survival was measured from the date of random assignment to death from any cause and was censored at the last follow-up date. Progression-free survival was measured from the date of random assignment to the first observation of disease progression or death from any cause if there was no progression. If there was no progression and the patient did not die, progression-free survival data were censored at the date on which the absence of progression was confirmed.

Table A1. Conditions Defining Patients As Unsuitable for Bolus Cisplatin Administration

Condition	No. of Patients	
	Docetaxel (n = 31)	Docetaxel/Cisplatin (n = 32)
Combination of more than one mild organ dysfunction, but violating none of the inclusion criteria	6	4
Combination of comorbid illness and mild organ dysfunction, but violating none of the inclusion criteria	5	8
Organ dysfunction not specified by the inclusion/exclusion criteria	8	3
Combination of more than one comorbid illness	1	7
Comorbid illness not specified by the exclusion criteria	2	2
Any other condition	9	8

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ORIGINAL ARTICLE

Therapeutic and preventive antiemetic effect of aprepitant in Japanese patients with thoracic malignancies who truly need it

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Abstract
Purpose Neurokinin-1 (NK-1) receptor antagonist is recommended for chemotherapy-induced nausea and vomiting (CINV) in highly emetogenic chemotherapy (HEC) and has recently been introduced to oncology practice in Japan. However, whether all patients undergoing HEC truly need NK-1 receptor antagonist remains unknown, and increasing medical costs due to uniform use of NK-1 receptor antagonist are a concern. This study was conducted to examine the prevalence of patients who needed aprepitant at the time of its introduction in Japan, and therapeutic and preventive effects of aprepitant on HEC or moderately emetogenic chemotherapy (MEC).
Patients and methods Eligible patients with thoracic malignancies who were to undergo HEC or MEC received 5-hydroxytryptamine receptor antagonists and dexamethasone to prevent CINV. Aprepitant was administered to treat CINV occurring in the first course, or to prevent CINV in the second course. Frequency of vomiting, degree of nausea, and quality of life with respect to CINV were assessed.
Results In total, 96 patients were enrolled. Aprepitant was not administered in 57 and 88 % of patients who received HEC and MEC, respectively. In patients treated with aprepitant (n=18), therapeutic use of aprepitant after occurrence of CINV (n=9) decreased average scores in numerical rating scale for nausea from 7.44 to 5.44 (p=0.10), and average frequency of vomiting per day from 2.11 to 0.11 (p=0.03). Prophylactic use of aprepitant in the second course (n=18) increased the proportion of patients with no significant nausea from 6 % (first course) to 50 % (second course; p=0.007), and those with no vomiting from 33 to 89 % (p=0.002). Aprepitant use also significantly improved quality of life with respect to CINV in the second course.
Conclusion More than half of patients receiving HEC and 88 % of patients receiving MEC did not use aprepitant. Aprepitant showed significant therapeutic and preventive effects on CINV in patients who truly needed it.

Keywords Aprepitant · Neurokinin-1 receptor antagonist · Chemotherapy-induced nausea and vomiting · Therapeutic effect · Prophylactic effect · Quality of life

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse event in patients treated with highly or moderately emetogenic chemotherapy (HEC or MEC). Cisplatin and carboplatin, which are key drugs in the treatment of thoracic cancer, frequently cause nausea and vomiting and

are classified as highly or moderately emetogenic agents. Nausea and vomiting not only reduce the quality of life of patients but also cause difficulty in oral ingestion, a serious problem that affects the continuation of treatment.

Vomiting is caused by stimulation of the vomiting center in the medulla oblongata. There are several pathways of vomiting stimulus conduction to the vomiting center: the path through chemoreceptor trigger zone in the fourth ventricle, afferent vagal nerve pathways from the gastrointestinal tract, and cerebral cortex induced by memories or impressions [1–3]. Neurokinin-1 (NK-1) receptor is highly expressed in the nucleus of the solitary tract, part of the vomiting center in the brainstem, and vomiting is induced by substance P binding to the receptor [2]. Aprepitant, an NK-1 receptor antagonist that became available in Japan in 2010, has been shown to have a preventive effect for nausea and vomiting induced by HEC. Aprepitant is also effective against delayed emesis, which is often difficult to control by conventional antiemetic treatment [4–6], and is recommended in guidelines for CINV in many countries [7–9]. The antiemetic guidelines classify anticancer agents by their emetogenicity into four categories—high, moderate, low, and the minimum emetogenic risk—and a three-drug preventive antiemetic combination comprising NK-1 receptor antagonist, 5-hydroxytriptamine (5-HT_3) receptor antagonist, and corticosteroid has been recommended for HEC and, if appropriate, for MEC. However, it is well known that CINV is controllable by conventional two-drug preventive antiemetic therapy that does not include NK-1 receptor antagonists in 40 to 70 % of patients treated by HEC [10–14]. In clinical practice, nausea and vomiting tend to be experienced the day after administration of anticancer agents with conventional preventive two-drug antiemetic therapy rather than on the day of administration. It has been reported that the release of substance P by anticancer agents increases on day 2 or later following chemotherapy [15, 16]; therefore, NK-1 receptor antagonist might be also effective on day 2 or later. While numerous reports have described prophylactic antiemetic effects of NK-1 receptor antagonists [8–12], to the best of our knowledge, a therapeutic effect of aprepitant after the occurrence of CINV has not been reported. Although the uniform prophylactic use of aprepitant is recommended in guidelines regardless of demographic risk factors, increased medical costs owing to uniform use of NK-1 receptor antagonists are a concern. When the current antiemetic guidelines were released following the approval of aprepitant in Japan, questions and concerns regarding how and whether the uniform prophylactic administration of aprepitant was truly needed were raised in the oncology clinic in Aichi Medical University Hospital. These questions prompted us to conduct this study to reveal the proportion of patients who truly need aprepitant, and to elucidate its therapeutic and preventive effect in patients who truly needed it.

Methods

This single institutional non-randomized prospective study was conducted after approval from the Institutional Review Board for Aichi Medical University School of Medicine.

Patients

Patients, aged 20 years or older, able to use the Japanese language, and receiving HEC or MEC for thoracic malignancies in the Division of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine, and who had given written informed consent before the onset of chemotherapy, were eligible.

Study design

All patients received standard antiemetic therapy consisting of intravenous granisetron and dexamethasone to prevent CINV. The prophylactic antiemetic regimen for HEC consisted of granisetron 1 mg intravenous (iv) and dexamethasone sodium phosphate 20 mg iv on day 1 before chemotherapy, and dexamethasone sodium phosphate 20 mg iv on days 2–3. The prophylactic antiemetic regimen for MEC consisted of granisetron 1 mg iv and dexamethasone sodium phosphate 12 mg iv on day 1 before chemotherapy, and dexamethasone sodium phosphate 8 mg iv on days 2–3. A patient who needed aprepitant was defined as a patient who experienced CINV and received aprepitant for therapeutic intent and/or received aprepitant for prophylactic intent in the subsequent courses of chemotherapy. Aprepitant was administered to patients who needed it to treat CINV in the first course when CINV occurred, or to prevent CINV in the second course. Aprepitant dose started at 125 mg on day 1, followed by 80 mg once a day orally, for a total of 3 days. All patients who experienced CINV in the first course received prophylactic aprepitant for the second course. Use of other antiemetic agents for rescue therapy was not limited.

Assessment

Patients completed the demographic questionnaire at onset of chemotherapy and kept a diary to monitor the antiemetic efficacy from day 1 to day 7. The diary documented vomiting episodes, use of rescue therapy, and daily nausea rating on a numerical rating scale (NRS): 0 indicated no nausea and 10 recorded nausea that was "as bad as it could be" [17]. They also completed the Functional Living Index-Emesis (FLIE) questionnaire Japanese version on day 6 [18]. Two pharmacists trained specifically for this study visited each patient on days 1 and 6 and, according to need, assisted them in the proper completion of the patient diary, reminded them to take

the study medication as directed, and reminded them to complete the FLIE questionnaire.

Efficacy was recorded form the initiation of chemotherapy infusion (0 h) to day 7 on chemotherapy. At post-initiation of chemotherapy, 0–24 and 24–144 h were defined as "acute" and "delayed" time frames, respectively, while 0–144 h was defined as the "overall" time frame. Patients who did not receive second course of chemotherapy were excluded from the efficacy analysis.

Efficacy of antiemetic therapy was evaluated as follows: (1) "no vomiting," no vomiting or retching; (2) "no rescue," no use of other antiemetics including dopamine D_2 receptor antagonist, histamine H_2 receptor blocker, proton pump inhibitor, histamine H_1 receptor blocker, and drip infusions to cover a reduced oral intake; (3) "no nausea," nausea of NRS=0; (4) "no significant nausea," nausea of NRS≤2; (5) "complete response," no vomiting and no use of rescue therapy during the overall time frame; and (6) "complete protection," no vomiting with no rescue therapy and nausea of NRS≤2.

Quality of life was assessed using the patient-reported FLIE questionnaire Japanese version. The FLIE questionnaire is a validated instrument for measurement of the impact of CINV on daily living, consisting of a nausea domain (nine items) and a vomiting domain (nine items) [18]. The questionnaire was administered on day 6, which is within the overall time frame. Responses to each question were rated on a 100-mm visual analog scale that was scored on a 1- to 7-point scale. For most items, the larger the score, the worse the effect on the patients' quality of life; the reverse was true for some items, for which the scores were reversed so that all items had the same direction.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Costs incurred for antiemetic medicines used during this study were estimated from clinical record data using the drug price for 2011. Antiemetic medicines included aprepitant, 5-HT_3 receptor antagonists, corticosteroids, and rescue medicines including dopamine D_2 receptor antagonists, histamine H_2 receptor blockers, proton pump inhibitors, histamine H_1 receptor blockers, and drip infusions to cover a reduced oral intake. All costs were converted from Japanese yen to US dollars based on Organization for Economic Co-operation and Development (OECD) purchasing power parity in 2013 ($1=¥100).

Statistical analysis

The primary objective of this study was to elucidate the prevalence of patients who needed aprepitant. The secondary objectives were therapeutic effects of aprepitant when it was administered after CINV occurred in the middle of the course, preventive effects of aprepitant on CINV when it was administered at the onset of the second course of HEC or MEC, and its impact on quality of life with respect to CINV. At least 65 patients were needed to ensure a 95 % confidence interval of ±20 % around the estimated prevalence of patients who needed aprepitant with a power of 0.8. The preventive effects of aprepitant for emesis were assessed in the overall phase (days 1–5), acute phase (day 1), and delayed phase (days 2–5). Wilcoxon signed-ranks test or paired t test was performed at a two-sided significance level of 0.05 to compare the therapeutic and prophylactic efficacy before and after administration of aprepitant and to compare the FLIE scores between patients who did and did not receive aprepitant. The Fisher's exact test was used to compare proportions of patients with the following: (1) no vomiting, (2) no rescue, (3) no nausea, (4) no significant nausea, (5) complete response, and (6) complete protection.

The prevalence of vomiting, nausea, and aprepitant usage for each factor of demographic background was evaluated using the Fisher's exact test. Univariate analyses were then performed to identify relationships between each factor of demographic background and the ratio of vomiting, nausea and aprepitant usage. Potential correlations between aprepitant usage and those demographic factors that had $p<0.15$ in the univariate analysis were evaluated using multivariate logistic regression. Results were defined as significant if p was <0.05, and 95 % confidence intervals (95 % CIs) were calculated.

Results

From June 2011 to January 2013, 96 patients were enrolled in the study, 77 of whom were assessable. Nineteen patients were excluded from the efficacy analysis because they did not receive the second course of chemotherapy because of adverse events ($n=12$), received aprepitant prophylactically from the first course ($n=1$), or failed to provide efficacy data ($n=6$). Patient characteristics are listed in Table 1. Twenty-eight patients received HEC containing cisplatin and 49 received MEC containing carboplatin, irinotecan, or amrubicine. Nine patients received aprepitant after CINV occurred in the first course and received it prophylactically in the second course; another 9 patients received aprepitant prophylactically at the onset of the second course and 59 patients did not receive aprepitant. Of patients who received HEC, 43 % used aprepitant, and only 12 % of patients who received MEC used aprepitant.

In nine patients who received aprepitant after CINV occurred in the first course of chemotherapy, the average frequency of vomiting reduced from 2.11 to 0.11 times/day ($p=0.03$). However, reduction of average NRS score for nausea was not significant (Fig. 1). The patient characteristics of

Table 1 Patient characteristics

	No. of patients	(%)
Age, years		
Median	67	
Range	38–85	
Gender		
Male	64	(83.1)
Female	13	(16.9)
Histology		
Lung	72	(93.5)
Adenocarcinoma	31	(40.3)
Squamous cell carcinoma	12	(15.6)
Large cell carcinoma	1	(1.3)
Non-small cell carcinoma	3	(3.9)
Small cell carcinoma	19	(24.7)
Others	6	(7.8)
Thymoma/thymic carcinoma	3	(3.9)
Cancer of unknown primary	2	(2.6)
Emetogenicity of chemotherapy		
High	28	(36.4)
Cisplatin doublet	21	(27.3)
Cisplatin doublet+bevacizumab	3	(3.9)
Cisplatin doublet+concurrent radiotherapy	4	(5.2)
Moderate	49	(63.6)
Carboplatin doublet	27	(35.1)
Carboplatin doublet+bevacizumab	4	(5.2)
Carboplatin doublet+concurrent radiotherapy	7	(9.1)
Single agent	11	(14.3)

those who needed aprepitant and those who needed no aprepitant did not differ significantly, except for the emetogenicity of chemotherapy used (HEC or MEC, Supplementary Table S1). Similarly, the patient characteristics of those who needed therapeutic aprepitant and those who did not need aprepitant at all or needed prophylactic-only aprepitant did not differ significantly, except for the emetogenicity of chemotherapy (Supplementary Table S2). These results support our observation of the therapeutic antiemetic effect of aprepitant after chemotherapy-induced vomiting occurred.

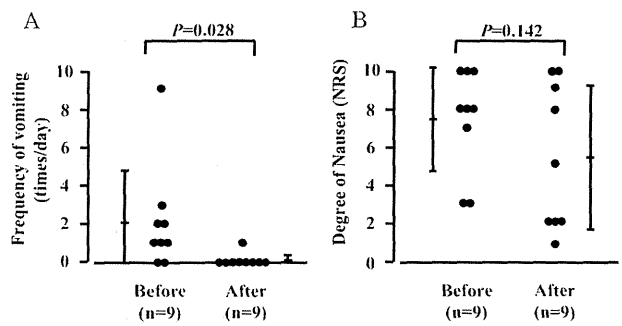

Fig. 1 Therapeutic effect of aprepitant added to the conventional antiemetic regimen consisting of 5-hydroxytriptamine (5-HT_3) receptor antagonists and dexamethasone on chemotherapy-induced vomiting (**a**) and nausea (**b**)

In patients who needed aprepitant, the prevalence of no vomiting, no rescue, no significant nausea, and complete response increased significantly in the delayed time frame in the second course, although the increment did not reach statistical significance in the acute time frame (Table 2). Average frequency of vomiting and average degree of nausea significantly reduced in the second course, except for frequency of vomiting in MEC (Table 3).

In patients who received HEC and needed aprepitant, the prevalence of no vomiting and no rescue significantly increased in the delayed time frame of second course (Table 2). In patients who received MEC and needed aprepitant, the prevalence of no rescue and no significant nausea in delayed time frame also significantly increased (Table 2).

The impact on daily living was assessed using the FLIE questionnaire. In patients who did not need aprepitant, the prevalence of patients with no impact on daily living (NIDL) was generally high and did not change during two courses of chemotherapy. In contrast, in patients who needed aprepitant, the prevalence of NIDL was low in the first course and significantly improved in the second course (Table 4).

Univariate analysis to assess the relationships between each demographic factor and vomiting, nausea and aprepitant usage, benzodiazepine usage, information from acquaintances regarding CINV, alcohol consumption, and defecation, the amount eaten at the last meal before chemotherapy and emesis risk of chemotherapy were extracted as risk factors of emesis. Incidence of vomiting was lower in patients who consumed less than half of their last meal before chemotherapy with marginal significance (p=0.05). Nausea occurred more frequently in patients who received HEC than those who received MEC (79 vs 49 %, p=0.02). Fewer patients who defecated every day used aprepitant compared with patients who did not (16 vs 45 %, p=0.01).

In multivariate analysis using a multiple logistic regression model, benzodiazepine use, information from acquaintances regarding CINV, and alcohol habit were used as variables. HEC was significantly correlated with nausea (odds ratio [OR] 4.38, 95 % CI 1.26–15.17, p=0.02) and aprepitant use (OR 5.47, 95 % CI 1.42–21.14, p=0.01), but insignificantly with vomiting (OR 2.21, 95 % CI 0.61–7.98, p=0.23). Benzodiazepine use was inversely correlated with aprepitant use (OR 0.16, 95 % CI 0.03–0.91, p=0.04).

Medical costs for antiemetic treatment during two courses of chemotherapy were evaluated. The mean costs of antiemetic treatment for patients who did not use aprepitant in the first and second courses were $7.6 and $8.7, respectively. For

Table 2 Efficacy end points

		No aprepitant needed (n=59)					Aprepitant needed (n=18)				
		Acute[b]		Delayed			Acute[b]		Delayed		
		1st course	2nd course	1st course	2nd course	p value[a]	1st course	2nd course	1st course	2nd course	p value[a]
Total	No vomiting (%)	100	100	88.1	91.5	0.762	77.8	100	44.4	88.9	0.012
	No rescue (%)	98.3	94.9	62.7	55.9	0.568	100	88.9	0	50.0	0.001
	No nausea (%)	89.8	88.1	59.3	57.6	1.000	44.4	50.0	0	11.0	0.486
	No significant nausea (%)	100	98.3	81.4	78.0	0.820	61.1	77.8	5.6	44.4	0.018
	Complete response (%)	100	98.3	78.0	76.3	1.000	55.6	77.8	5.6	38.9	0.041
	Complete protection (%)	98.3	93.2	57.6	50.8	0.580	55.6	50.0	0	16.7	0.229
HEC	No vomiting (%)	100	100	87.5	93.8	1.000	75.0	100	50.0	100	0.014
	No rescue (%)	100	93.8	56.3	43.8	0.724	100	83.3	0	41.7	0.037
	No nausea (%)	87.5	87.5	43.8	43.8	1.000	16.7	41.7	0	8.3	1.000
	No significant nausea (%)	100	100	62.5	68.8	1.000	41.7	83.3	16.7	33.3	0.640
	Complete response (%)	100	100	75.0	68.8	1.000	41.7	83.3	8.3	33.3	0.317
	Complete protection (%)	100	93.8	56.3	37.5	0.479	41.7	50.0	0	8.3	1.000
MEC	No vomiting (%)	100	100	88.4	90.7	1.000	83.3	100	33.3	66.7	0.567
	No rescue (%)	97.7	95.3	67.4	65.1	1.000	100	100	0	66.7	0.061
	No nausea (%)	90.7	88.4	65.1	62.8	1.000	100	66.7	0	16.7	1.000
	No significant nausea (%)	100	71.2	61.0	59.3	1.000	100	66.7	0	66.7	0.061
	Complete response (%)	100	97.7	79.1	79.1	1.000	83.3	66.7	0	50.0	0.182
	Complete protection (%)	97.7	93.0	58.1	55.8	1.000	83.3	50.0	0	33.3	0.455

No nausea = nausea score 0; no significant nausea = nausea score 0, 1, 2 by NRS; complete response = no vomiting and no significant nausea; complete protection = no vomiting, no significant nausea, and no rescue therapy

HEC highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy

[a] Result of statistical analysis by Fisher's exact test compared with incidence of each item in the first course and second course of delayed phase were shown in p value columns

[b] There was no statistical significance in incidence in all of items in acute phase

patients who needed aprepitant after CINV occurred in the first course and prophylactically in the second course, the average total cost of medicines for antiemetic treatment was $156.9 in the first course and $165.8 in the second course. In patients

Table 3 Prophylactic effect of aprepitant on chemotherapy-induced nausea and vomiting

	No aprepitant needed (n=59)			Aprepitant needed (n=18)		
	1st course	2nd course	p value	1st course	2nd course	p value
Total (n=77)						
Frequency of vomiting	0.20±0.64	0.15±0.61	0.594	1.50±2.12	0.11±0.32	0.014
Degree of nausea	1.37±1.91	2.33±0.61	0.789	6.94±2.94	3.00±2.85	0.027
HEC (n=28)						
Frequency of vomiting	0.25±0.77	0.06±0.25	0.383	1.75±2.49	0.00±0.00	0.010
Degree of nausea	1.94±2.21	2.00±2.37	0.864	6.58±3.03	3.17±2.48	0.033
MEC (n=49)						
Frequency of vomiting	0.19±0.59	0.19±0.70	1.000	1.00±1.10	0.33±0.52	0.175
Degree of nausea	1.16±1.77	1.23±2.31	0.829	7.50±2.88	2.67±3.72	0.024

Frequency of vomiting (times/day) and degree of nausea measured by NRS were extracted from emesis diary patients recorded, and the worst point was used for calculating average. Statistical analysis was performed by pared t test (mean ± SD)

HEC highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy

Table 4 Patients with "no impact on daily life" by chemotherapy-induced nausea and vomiting

	No aprepitant needed (n=59)			Aprepitant needed (n=18)		
	1st course	2nd course	p value	1st course	2nd course	p value
Total (%)	83.1	84.7	>0.999	16.7	55.6	0.035
Frequency of vomiting (%)	91.5	94.9	0.717	44.4	94.4	0.003
Degree of nausea (%)	74.6	76.3	>0.999	11.1	44.4	0.060

"No impact on daily life" by CINV was defined as an FLIE score of no less than 2 in each item. Statistical analysis was performed by Fisher's exact test

who received prophylactic aprepitant only in the second course, the mean total cost of medicines for antiemetic treatment increased from $21.7 in the first course to $115.5 in the second course (Fig. 2).

Discussion

Antiemetic guidelines recommend a combination of three antiemetics including NK-1 receptor antagonist to prevent CINV induced by HEC [7–9]. However, it has been reported that approximately half of patients who received HEC and a conventional antiemetic regimen without NK-1 receptor antagonists did not experience CINV. Our study has revealed that more than half of patients who received HEC and nine tenths of patients who received MEC did not need aprepitant and that in patients who truly needed aprepitant, it exerted remarkable therapeutic and preventive effect against CINV. This is the first report to elucidate the therapeutic effect of aprepitant on CINV; aprepitant was effective not only for prevention but also for treatment of CINV.

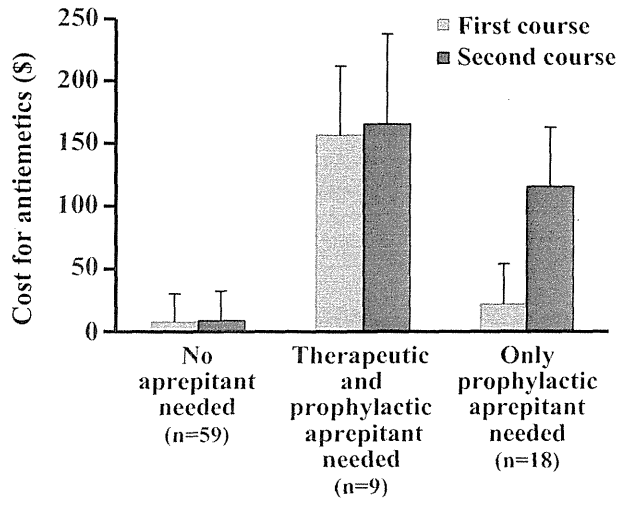

Fig. 2 Total medical cost of antiemetic therapy in patients who needed no aprepitant, both therapeutic and prophylactic aprepitant, or only prophylactic aprepitant. Medical costs included dopamine D_2 receptor antagonists, histamine H_2 receptor blockers, proton-pump inhibitors, histamine H_1 receptor blockers, laxative agents, and drip infusions to cover a reduced oral intake

In more than half of patients who received HEC and approximately 90 % of patients who received MEC, CINV was fairly well controlled without aprepitant. Two thirds of patients who received aprepitant after CINV occurred experienced disappearance of vomiting and reduction of nausea regardless of the type of chemotherapy, HEC or MEC. Frequency of vomiting and the worst degree of nausea reduced by prophylactic administration of aprepitant in the second course. Total FLIE scores also reduced with prophylactic administration of aprepitant in the second course, indicating improved quality of life. These results suggest that aprepitant is highly effective for patients who truly need it.

Antiemetic guidelines recommend aprepitant use from the first course for patients receiving HEC because of the concern that anticipatory emesis before the second course might be induced by a negative experience of CINV in the first course. In this study, however, no patients experienced nausea and vomiting before starting chemotherapy, suggesting that anticipatory emesis did not influence the study results. Vomiting of delayed phase remained in 11.1 % of aprepitant-needed patients, and it was thought to be mostly breakthrough emesis. It has been reported that younger age, female sex, experience of morning sickness during pregnancy, and a previous experience of CINV are risk factors of emesis, while regular alcohol intake inversely correlates with CINV [19–28]. The influence of patients' demographic background on CINV is not clearly understood, and a demographic-background-based antiemetic strategy is not recommended in the CINV guidelines. Here, we identified benzodiazepine use as the only significant negative demographic factor for aprepitant use. Although younger age, female sex, experience of morning sickness during pregnancy, and a previous experience of CINV have been reported as risk factors, we failed to show a significant correlation of these factors with CINV, indicating that we are unable to identify patients who need aprepitant before starting emetogenic chemotherapy.

In this study, we did not limit the use of additional medications that might have antiemetic effects, such as dopamine D_2 receptor antagonists, histamine H_2 receptor blockers, proton pump inhibitors, histamine H_1 receptor blockers, laxative

agents, and drip infusions to cover a reduced oral intake. These additional antiemetics were not administered at the same time with aprepitant to discriminate their antiemetic effect from that of aprepitant. While these medications might be related to the apparently low complete response rate, it also probably assisted aprepitant in reducing CINV. Regarding the therapeutic effects of aprepitant, the following limitations of this study should also be noted. First, it is difficult to demonstrate the therapeutic effect of aprepitant during the same course of the chemotherapy because a placebo effect cannot be excluded. In order to truly prove the therapeutic effect of aprepitant, a placebo-controlled randomized trial (aprepitant vs placebo) is needed. Second, we did not limit the use of additional medications with aprepitant, and we cannot completely exclude their effects. Third, chemotherapy-induced emesis naturally gradually reduces as time goes on, and the improvement of CINV as a result of natural time course cannot clearly be distinguished from therapeutic effects of aprepitant.

Economic concerns regarding the uniform use of aprepitant might reduce aprepitant prescription, leading to low compliance with antiemetic guidelines. Daniel et al. reported a compliance rate of only 10 % with aprepitant, unlike the compliance rates of 60–90 % seen with 5-HT_3 receptor antagonists and dexamethasone [29]. Cost-effectiveness of aprepitant is an issue under debate. Lordick et al. and Annemans et al. reported that aprepitant-based strategy is more effective and less expensive compared with standard care [30, 31]. However, Moore et al. reported that aprepitant provides only modest benefit and would be cost-effective only when the likelihood of delayed CINV or the cost of rescue medications is high [32]. We calculated the total drug cost for antiemetic therapy in the first two courses of chemotherapy. The significant difference in total cost of antiemetics between patients who did and did not need aprepitant was due to the cost of aprepitant and rescue medications. Patients who did not experience CINV on conventional two-drug antiemetics did not need further medical expense with CINV treatment, and their quality of life was not influenced by CINV. On the other hand, patients who needed aprepitant required further antiemetic therapy, and their quality of life was considerably disturbed by CINV. As we have shown in this study, aprepitant is highly effective against CINV especially for those who truly need it. However, considering that we have no effective screening methods to identify those patients before chemotherapy, we agree to follow the current antiemetic guidelines recommending uniform use of aprepitant, at least when prescribing HEC chemotherapy. The results from our study warrant further research to discriminate, before chemotherapy, patients who need extensive antiemetic treatment against CINV and those who do not.

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

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