Conclusions: The interpretation of study results is limited due to early stopping. Further study is needed to confirm survival benefit of platinum-based chemotherapy for elderly non-small-cell lung cancer [UMIN-CTR (www.umin.ac.jp/ctr/) ID: C000000146].

Key words: cisplatin, docetaxel, elderly, non-small-cell lung cancer, interim analysis

Introduction

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related death in most developed countries (1). The rapid expansion of the elderly population in the majority of industrialized nations has resulted in a significant increase in the number of older patients diagnosed with NSCLC. Platinum-based doublet chemotherapy is considered the standard of care for fit patients with advanced NSCLC (2). Retrospective subset analyses of the trials involving young and elderly patients with no upper age limit have reported that elderly NSCLC patients with good performance status tolerate platinum-based combination chemotherapy well and achieve survival benefits similar to those of younger patients (3–6). However, elderly patients are under-represented in these clinical trials, making it difficult to extrapolate these results to elderly population, in general (7,8). Aging is associated with a number of physiological changes, such as deterioration of renal and liver function and decreased bone marrow reserves, which affect the tolerability and outcomes of cytotoxic chemotherapy (9,10). In addition, the presence of comorbid illnesses needs to be considered when caring for elderly patients (11). The 2004 American Society of Clinical Oncology guidelines recommended use of vinorelbine or gemcitabine monotherapy for elderly patients with advanced NSCLC (12) based on evidence from two Phase III trials specific for elderly patients (13,14). In addition, a Japanese Phase III study evaluating the role of docetaxel (D) monotherapy for elderly advanced NSCLC had demonstrated equivalence, if not superiority, for D to vinorelbine (15). In an effort to develop more effective treatments, the role of platinum-doublet has been evaluated employing attenuated platinum doses or carboplatin instead of cisplatin to achieve feasible therapeutic indices in elderly patients (16–18). A Japanese Phase II study evaluating the combination of weekly D and cisplatin in 33 patients ≥75 years old resulted in a response rate of 52%, median survival of 15.8 months, and an acceptable toxicity profile (19). This promising result led us to plan the current randomized Phase III study. We selected D, an agent used in the above-mentioned Phase II study (19), instead of vinorelbine or gemcitabine, as a control arm in order to evaluate clearly whether the addition of cisplatin to single-agent chemotherapy could improve survival for elderly patients.

Patients and methods

Study design

Patients who met all eligibility criteria were randomly allocated to receive one of the two regimens in equal proportion, as follows: arm A, D 25 mg/m^2 infused over 60 min on Days 1, 8 and 15; and arm B, D 20 mg/m^2 infused over 60 min plus cisplatin 25 mg/m^2 infused over 15–20 min on Days 1, 8 and 15.

Registration was made by telephone or fax to the Japan Clinical Oncology Group (JCOG) Data Center. Patients were randomized by the minimization method balancing the arms with institution, stage of disease (III versus IV) and age (≥75 versus ≤74 years). Treatment cycles for both treatment arms were repeated every 4 weeks

until unacceptable toxicity or disease progression. Guidelines for dose adjustments were provided for chemotherapy-related toxicity. Dexamethasone and 5-HT$_3$ antagonist as antiemetic agents and 1000–1500 ml fluid infusion were recommended for patients assigned DP. No other chemotherapy, radiotherapy or experimental medication was permitted while the patient was under study and appropriate supportive care was provided. Radiographic tumor evaluation was carried out at least every two cycles and toxicity was assessed before every cycle.

Patient selection

Patients with histologically or cytologically confirmed diagnosis of Stage IIIA/IIIB (ineligible for definitive radiotherapy) or Stage IV NSCLC were enrolled in this study. All patients were required to be ≥70 years old with an ECOG performance status of 0 or 1, and adequate hematological, renal (serum creatinine ≤1.2 mg/dl) hepatic and respiratory functions. Previous surgery was allowed if it had been completed at least 4 weeks before inclusion. No prior radiotherapy for primary lesion was allowed. Patients eligible for 1 day bolus administration of cisplatin after considering renal and cardiac function and comorbid illnesses, or patients receiving prior chemotherapy were excluded from participation. This study protocol was reviewed and approved by the Protocol Review Committee of JCOG and the institutional review board at each participating institutions prior to initiation of the study, and the study was conducted in accordance with the precepts established in the Declaration of Helsinki. Patients who were eligible for participation provided written informed consent before undergoing any study procedure.

Statistical analysis

The trial was designed as a multicenter, prospective, randomized Phase III study. The primary endpoint for this trial was overall survival (OS). Secondary endpoints included response rates, progression-free survival (PFS), symptom score and toxicity.

The primary objective was to determine whether addition of cisplatin to monotherapy could improve survival for elderly patients with NSCLC. The study was designed with an 80% power using a one-sided alpha of 0.025 to detect a 50% increase in median survival from 7 months with D to 10.5 months with docetaxel plus cisplatin (DP). As a result, 220 patients (110 patients per arm) accrued in a 3-year period with a 1-year follow-up were required (20). Assuming a proportion of ineligible and lost to follow-up of 5%, sample size for the study was set at 230 patients. OS, PFS and response were assessed using the total eligible population. OS was measured from the date of randomization to the date of death from any cause and censored at the last follow-up date. PFS was measured from the date of randomization to the date of the first observation of disease progression, or the date of death from any cause if no progression had been identified. If there was no progression and if the patient had not died, data on PFS were censored as of the date on which the absence of progression was confirmed. Survival and PFS curves were estimated using the Kaplan–Meier method and compared using the stratified log-rank

test with age and stage as stratification factors. Hazard ratios of treatment effect were estimated using Cox proportional hazard modeling.

The first interim analysis was planned to confirm that response rate for the control arm was sufficiently high. Second and third interim analyses were planned for the primary endpoint of OS with adjustment for multiple comparisons taken into account according to the method of Lan and DeMets (21). The O'Brien Fleming-type alpha spending function was used. The second interim analysis was planned for the date on which half of the planned number of patients had been enrolled, and the third interim analysis was planned after the date on which all patients had been enrolled.

Response evaluation was performed according to Response Evaluation Criteria In Solid Tumors (22). Safety of the treatment regimens was assessed by calculating the percentage of patients experiencing Grade 3 or 4 toxicity using National Cancer Institute Common Toxicity Criteria version 2.0. Symptom score was assessed with the seven-item disease-specific subscale in the FACT-L (Functional Assessment of Cancer Therapy-Lung) (23) by patients themselves before treatment and 8 weeks later. The sum of the scores for all seven items was compared between the baseline and post-treatment assessments. The maximum attainable score was 28, with which the patient was considered to be asymptomatic. We calculated the difference between the baseline and post-treatment scores in each patient and compared them across treatment groups by analysis of covariance (ANCOVA) with baseline score as a covariate. If the post-treatment score was above the baseline score, the symptom score for that patient was judged as having shown improvement.

The P value for the primary analysis was presented one-sided in accordance with the trial design, while other values were two-sided. All analyses were carried out using SAS version 9.1 software (SAS, Cary, NC, USA).

Results

Figure 1 summarizes patient disposition in the trial. Enrollment into the study began in April 2003 and the study was terminated in April 2006. A total of 126 patients from 20 institutions in JCOG were enrolled and randomly assigned. All patients received study treatment; thus, all 126 patients were included in the safety analysis population.

However, since one patient in the D group was ineligible due to prior radiotherapy for brain metastases within 2 weeks before accrual, that patient was excluded from the efficacy analyses.

Patient characteristics

Baseline characteristics of patients were similar in the two treatment groups as a whole except that more patients in the monotherapy group had cerebrovascular diseases and diabetes as comorbid diseases (Table 1). More patients with non-squamous histology were identified in the DP arm than in the D arm especially in the subgroup between 70 and 74 years old. Whereas the percentage of patients with Stage III without pleural effusion was larger in the D arm than in the DP arm in the subgroup between 70 and 74 years old. Diabetes was significantly more frequent in patients assigned to D arm than in those assigned to DP arm as a whole and in the subgroup between 70 and 74 years old.

Dose administration

Overall, 30 (47.6%) of 63 patients in the D arm and 40 (63.5%) of 63 patients in the DP arm received four or more cycles of chemotherapy. The median number of treatment cycles was 3.0 and 4.0 cycles, respectively (D range 1–8 cycles; DP range 1–7 cycles). The percentages of patients who received more than six cycles were 15.9% for D and 6.3% for DP arm. The major reasons for ending treatment in the D and DP arms were disease progression (68 and 41%, respectively), adverse events (13 and 19%, respectively) and patient refusal related to toxicity (11 and 32%, respectively). The toxicities that did not meet the criterion for stopping study treatment but led to study discontinuation were mostly ≤Grade 3 fatigue, anorexia, nausea and diarrhea. However, 40% of the patients who refused the treatment continuation for some reasons related to toxicity completed four or more cycles and 70% of them completed three or more cycles.

Efficacy

The second planned interim analysis was performed on 112 assessable patients (D/DP, $n = 56$ each; ≤74 years/≥75 years, 39/61%; male/female, 77/23%; III/IV, 30/70%) in March 2006. Information time, defined as the proportion of interim events to the planned events,
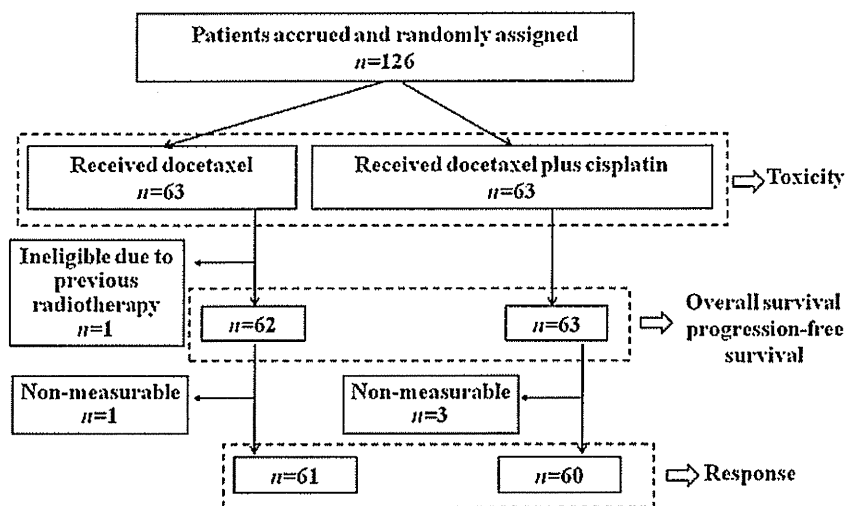

Figure 1. Patient disposition.

Table 1. Patient characteristics

Age, years	Docetaxel			Docetaxel + cisplatin		
	≤74	≥75	All	≤74	≥75	All
No. of patients	25	38	63	24	39	63
Characteristic						
Age, years						
Median	72	77	76	73	77	76
Range	70–74	75–88	70–88	70–74	75–86	70–86
Gender, *n* (%)						
Male	20 (80)	29 (76)	49 (78)	15 (62)	33 (85)	48 (76)
Female	5 (20)	9 (24)	14 (22)	9 (37)	6 (15)	15 (24)
Performance status, *n* (%)						
0	11 (44)	12 (32)	23 (37)	12 (50)	14 (36)	26 (41)
1	14 (56)	26 (68)	40 (63)	12 (50)	25 (64)	37 (59)
Disease stage, *n* (%)						
III	10 (40)	10 (26)	20 (32)	5 (21)	14 (36)	19 (30)
With pleural effusion	3 (12)	6 (16)	9 (14)	2 (8)	3 (8)	5 (8)
Without pleural effusion	7 (28)	4 (10)	11 (17)	3 (12)	11 (28)	14 (22)
IV	15 (60)	28 (74)	43 (68)	19 (79)	25 (64)	44 (70)
Histology, *n* (%)						
Squamous	11 (44)	14 (37)	25 (40)	5 (21)	13 (33)	18 (29)
Non-squamous	14 (56)	24 (63)	38 (60)	19 (79)	26 (67)	45 (71)
Weight loss, *n* (%)	5 (20)	11 (29)	16 (25)	6 (25)	11 (28)	17 (27)
Prior surgery, *n* (%)						
Primary lesion	2 (8)	0	2 (3)	1 (4)	6 (15)	7 (11)
Comorbid illness, *n* (%)						
Cardiovascular	1 (4)	2 (5)	3 (5)	2 (8)	2 (5)	4 (6)
Respiratory	3 (12)	4 (10)	7 (11)	3 (12)	4 (10)	7 (11)
Digestive/hepatic	0	2 (5)	2 (3)	2 (8)	2 (5)	4 (6)
Cerebrovascular	0	5 (13)	5 (8)	0	0	0
Diabetes	7 (28)	2 (5)	9 (14)	2 (8)	0	2 (3)

was 0.26 (49/191). As the one-sided P value ($P = 0.00515$) from the stratified log-rank test by age and stage was not lower than the multiplicity-adjusted bound of 0.0000096 for interim analyses, the formal criterion for suspending the trial was not met. However, subgroup analyses of age, one of the adjustment factors for randomization showed that OS was markedly worse in D than in DP (hazard ratio for DP over D, 0.23; 95% confidence interval (CI), 0.09–0.62) for the subgroup of 70–74 years old, although no significant difference between treatment arms was detected (hazard ratio, 0.72; 95%CI, 0.35–1.49) for patients ≥75 years old. The P value for interaction between subgroup by age and treatment arms was $P = 0.077$, indicating that D may be disadvantageous for the subgroup between 70 and 74 years old (Fig. 2). The Data and Safety Monitoring Committee (DSMC, one of the standing committees of JCOG, 20 members except for the investigators of this study) participated the review) recommended study termination and disclosure of the results, although no rule to reach this decision had been pre-specified in the protocol. The final analysis was performed on 125 eligible patients in February 2007. Subgroup analyses of age in the final analyses also showed that OS was worse in D than in DP (hazard ratio for DP over D, 0.508; 95% CI, 0.259–0.997) for the subgroup of 70–74 years old, whereas no significant difference between treatment arms was detected (hazard ratio 0.822; 95%CI, 0.483–1.400) for patients ≥75 years old. However, the P value for interaction between subgroup by age and treatment arms became $P = 0.45$.

Overall response rates in 121 patients significantly favored DP (55.0%) over D (26.2%; $P = 0.0016$ by Fisher's exact test; Table 2). The difference was larger in patients 70–74 years old (DP, 69.6%; D, 16.7%) than in patients ≥75 years old (DP, 45.9%; D, 32.4%).

By 13 February 2007, a total of 91 (72.8%) of the 125 eligible patients had died (DP, $n = 45$; D, $n = 46$). For DP and D, median survival times was 17.0 months and 10.7 months and 1-year survival rates were 66.6 and 45.2%, respectively (two-sided $P = 0.0384$, log-rank test) (Fig. 3). The difference was larger in patients 70–74 years old (DP, 24.0 months, 78.9%; D, 9.9 months, 45.8%) than in patients ≥75 years old (DP, 13.6 months, 59.0%; D, 11.5 months, 44.7%) (Table 2). Median progression-free times for DP and D were 6.2 months and 3.7 months, and one-year PFS rates were 10.9 and 5.0%, respectively (two-sided $P = 0.0004$, log-rank test) (Fig. 3). The difference was on the contrary larger in patients ≥75 years old (DP, 6.2 months, 12.7%; D, 3.6 months, 5.3%) than in patients 70–74 years old (DP, 6.1 months, 8.3%; D, 4.1 months, 4.6%) (Table 2).

Toxicity

Grades 3 and 4 hematological and non-hematological events are summarized in Table 3. No Grade 4 hematological toxicity was encountered in either arm. Grade 4 hyponatremia occurred in only one patient receiving D. Overall toxicity in both treatment arms was generally mild and well-tolerated in elderly patients.

One patient developed treatment-related interstitial pneumonia after four cycles of DP; despite steroid treatment, the patient died from this toxicity on Day 102 after the last treatment.

Symptom score

Baseline symptom score data were available for all 126 patients. Symptom score data at 8 weeks later were missing in six surveys due to death, severe impairment of general condition or refusal to participate.
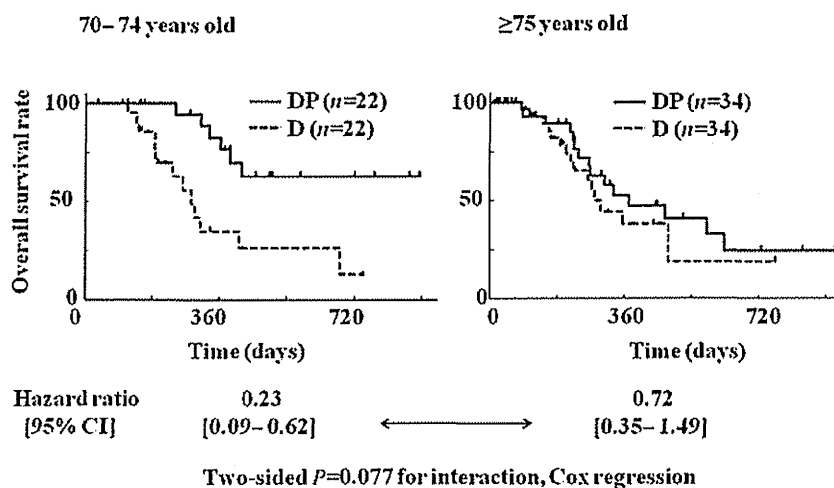
Figure 2. Overall survival by age subgroup at the second interim analysis. DP, docetaxel plus cisplatin; D, docetaxel; CI, confidence interval.

Table 2. Clinical efficacy data at final analysis

	Docetaxel			Docetaxel + cisplatin		
Age, years	≤74	≥75	All	≤74	≥75	All
No. of patients	24	37	61	23	37	60
Response						
Complete response	0	0	0	1	0	1
Partial response	4	12	16	15	17	32
Stable disease	13	8	21	6	12	18
Progressive disease	6	15	21	1	5	6
Not assessable	1	2	3	0	3	3
Overall response rate (%)	16.7	32.4	26.2	69.6	45.9	55.0
(95% CI)[a]			(20.0–47.5)			(52.5–80.1)
Progression-free survival (median, months)	4.1	3.6[b]	3.7[c]	6.1[d]	6.2[e]	6.2[f]
Overall survival (median, months)	9.9	11.5[b]	10.7[c]	24.0[d]	13.6[e]	17.0[f]

[a]$P = 0.0016$.
[b]$n = 38$.
[c]$n = 62$.
[d]$n = 24$.
[e]$n = 39$.
[f]$n = 63$.

Deterioration of symptom score from baseline was observed in both treatment arms; the least square mean scores at baseline and 8 weeks were 19.7 and 19.4 for D arm and 20.1 and 19.0 for DP arm. There was no significant difference between the treatment arms (two-sided, $P = 0.564$, ANCOVA with baseline score as a covariate).

Discussion

This randomized study was conducted based on promising response and survival data from a Japanese Phase II study (19). A weekly D schedule (24) was selected as a control regimen instead of the tri-weekly schedule widely used in our country to facilitate the interpretation of study results. In addition, a previous study comparing the two schedules of D for elderly patients with advanced NSCLC reported a trend toward longer survival using a weekly regimen (25).

The tolerability profile particularly in terms of hematological toxicities, was also more favorable with the weekly regimen. Weekly D as a second-line treatment for advanced NSCLC has been shown to offer similar efficacy to the tri-weekly schedule, with significantly less febrile neutropenia in a meta-analysis of five randomized trials (26). A recently reported prospective trial compared D (38 mg/m², on Day 1 and 8, every 3 weeks) with vinorelbine (25 mg/m², on Day 1 and 8, every 3 weeks) in 130 NSCLC patients aged ≥65 years (27). Although this trial was closed prematurely because of low accrual, it suggested that weekly D could have an efficacy comparable with that of vinorelbine as first-line treatment in elderly patients with advanced NSCLC.

Weekly D was considered the most appropriate control regimen, but, no published data from Phase II studies with the same dose (25 mg/m²) were available at the time of planning this study, so, we planned a first interim analysis to confirm that the dose of weekly D
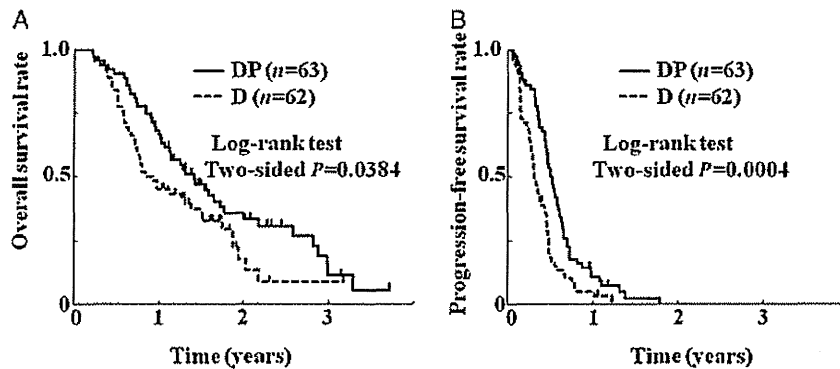
Figure 3. Overall survival (A) and progression-free survival (B) at the final analysis.

Table 3. Toxicities

Type of toxicity	Docetaxel ($n = 63$)		Docetaxel + cisplatin ($n = 63$)	
	Grade3 $\leq74/\geq75$	Grade4 $\leq74/\geq75$	Grade3 $\leq74/\geq75$	Grade4 $\leq74/\geq75$
Hematologic events, (%)[a]				
Leukopenia	0.0/5.3	0	4.2/7.9[b]	0
Neutropenia	4.0/5.3	0	16.7/13.2[b]	0
Febrile neutropenia	0	0	4.2/5.1	0
Thrombocytopenia	0	0	0	0
Anemia	0.0/2.6	0	20.8/13.2[b]	0
Non-hematologic events, (%)[a]				
AST	4.0/2.6	0	0	0
ALT	4.0/2.6	0	0	0
Creatinine	0	0	0	0
Nausea	8.0/5.3	–	12.5/7.7	–
Vomiting	4.0/0.0	0	0	0
Infection	12.0/10.5	0	4.2/10.3	0
Diarrhea	0	0	4.2/7.7	0
Hyponatremia	12.0/2.6	0.0/2.6	12.5/7.9[b]	0
Pneumonitis	0.0/2.6	0	4.2/2.6	0

[a]% Percentage for each age subgroups: docetaxel ≤74 ($n = 25$), ≥75 ($n = 38$), docetaxel + cisplatin ≤74 ($n = 24$), ≥75 ($n = 39$).

[b]Data were not obtained from one patient.

was sufficiently efficacious to allow study continuation. The response rate at the first interim analysis was superior to the pre-specified threshold, at over 10%, so, the patient accrual was continued.

At the second interim analysis, an unexpectedly large difference in OS was observed for the 70- to 74-year-old subgroup, one of the strata in stratified log-rank test. The DSMC recommended early termination of the study on ethical grounds to avoid possible disadvantages in 70- to 74-year-old patients allocated to the D arm. This DSMC recommendation was difficult to agree for the group investigators, since the decision was not based on a pre-specified rule. However, the group investigators finally accepted the DSMC recommendation because efficacy of the control arm may have been insufficient due to low doses (25 mg/m^2/week) of D for the subgroup of younger age. Since the percentage of patients with diabetes was larger in the D arm than that in the DP arm in the subgroup of 70- to 74-year old, comorbid illness might have influenced survival difference. Other possible reasons for the unexpectedly large difference in survival between treatment arms for the subgroup of 70- to 74-year old may include: (i)

chance occurrences due to the small sample size; (ii) imbalances in unexamined baseline prognostic factors, such as epidermal growth factor receptor (EGFR) mutations; or (iii) imbalances in post-protocol treatment, such as the use of gefitinib as a second-line treatment. As more patients with non-squamous histology were identified in the DP arm than in the D arm for the subgroup between 70 and 74 years old, more patients harboring EGFR mutation might have been included in the DP arm than in the D arm. The two retrospective analyses showed that the patients with EGFR gene mutations, compared with patients with wild-type EGFR, had increased survival and response rates in the patients treated by gefitinib, but also in those treated by D (28,29). However, data for possibilities (i) and (iii) were not collected in this study although those were important information, and discriminating between these possibilities is difficult without future clinical trials.

Recent prospective Phase III trial reported by a French group randomly assigned 451 NSCLC patients aged 70–89 years to either carboplatin and weekly paclitaxel doublet chemotherapy or monotherapy (vinorelbine or gemcitabine) (30). This is the first study to demonstrate a benefit of platinum-based doublet therapy in elderly patients with advanced NSCLC. Based on the results, EORTC Elderly Task Force, Lung Cancer Group and International Society of Geriatric Oncology recommended that prospective trials support the use of carboplatin-based doublets in fit elderly patients, while for less fit patients single-agent treatment represent a valid option (31).

The promising survival and response data and favorable toxicity profile seen in the Phase II study (19) were reproduced with the DP arm in this study again. As the evaluation of this modified platinum-doublet regimen for elderly patients seemed to remain of interest, we launched a new study to compare weekly D and cisplatin with tri-weekly D, which has been demonstrated to be effective and tolerable in elderly patients with advanced NSCLC in other Japanese Phase III study (15). However, this trial was also terminated early after the first planned interim analysis, based on the DSMC recommendation that the predictive probability that weekly D and cisplatin would be superior to tri-weekly D at the time of the final analysis was very low, and failed to demonstrate any advantage of the addition of cisplatin to single-agent D for elderly advanced NSCLC patients (32).

In conclusion, the interpretation of study results was limited, since this study was prematurely closed based on a strong interaction that cisplatin-doublet may be advantageous for the subgroup of patients aged 70–74 years. No new data regarding the superiority of cisplatin-based doublets over monotherapy in fit elderly patients with advanced NSCLC were published yet.

Study identification numbers

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Conflict of interest statement

Tomohide Tamura has received honoraria from Sanofi, Bristol-Myers KK. The other authors declare that they have no conflict of interest.

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JOURNAL OF CLINICAL ONCOLOGY

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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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 $\geq$ 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 $\geq$ 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]

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/m² infused over 60 minutes on day 1 every 3 weeks) or the DP arm (docetaxel 20 mg/m² infused over 60 minutes plus cisplatin 25 mg/m² 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 α = .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
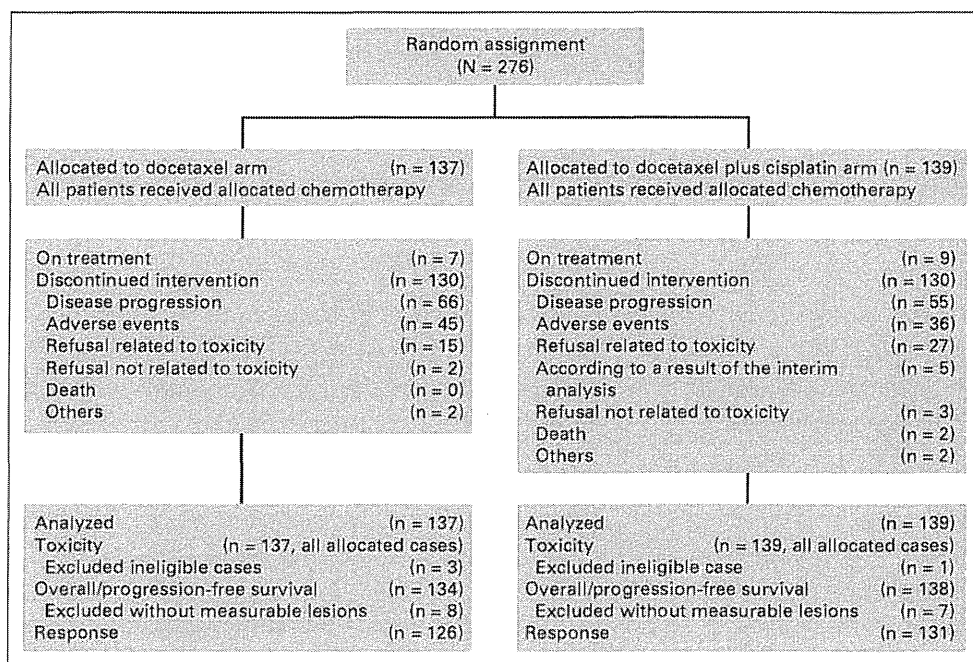
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Fig 1. CONSORT diagram.

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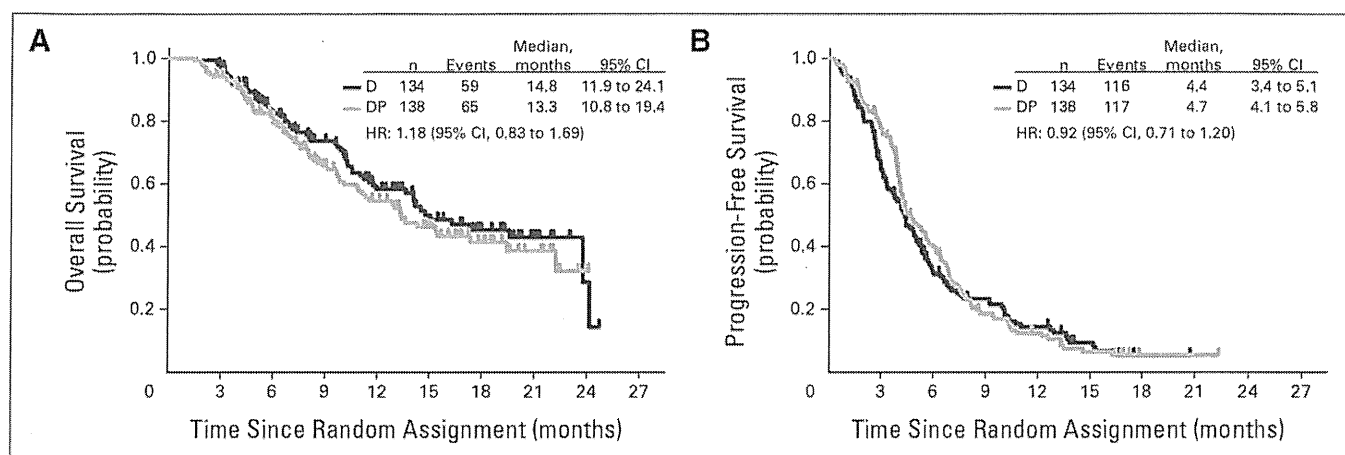
Fig 2. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival. Tick marks indicate censored patients at the data cutoff point (November 2010). D, docetaxel; DP, docetaxel plus cisplatin; HR, hazard ratio.

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 $\geq$ 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 $\geq$ 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						
Adverse Event	Docetaxel (n = 137)			Docetaxel/Cisplatin (n = 139)		
	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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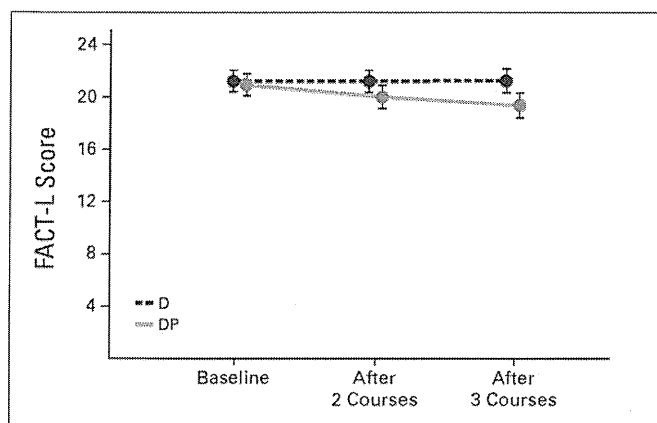
Fig 3. Quality-of-life assessments according to the seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L). Dots and error bars indicate the least squared mean total scores and 95% CI, respectively. Higher scores indicate a better quality of life. D, docetaxel; DP, docetaxel plus cisplatin.

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).
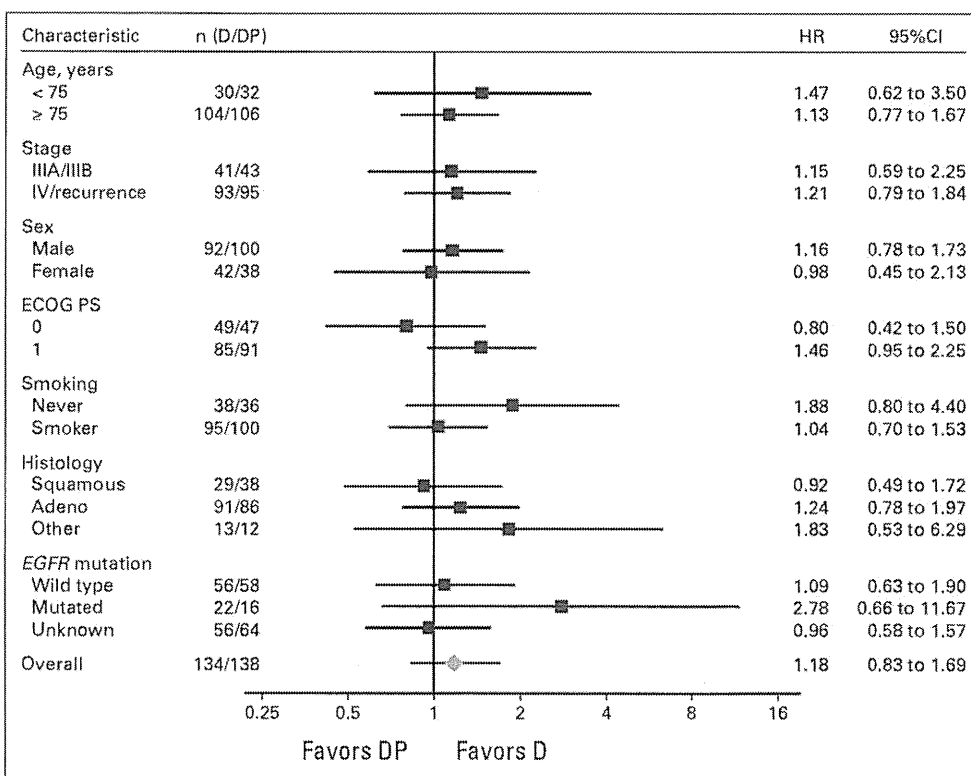
Supplementary Ad Hoc Analysis

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.

Characteristic	n (D/DP)	HR	95%CI
Age, years			
< 75	30/32	1.47	0.62 to 3.50
≥ 75	104/106	1.13	0.77 to 1.67
Stage			
IIIA/IIIB	41/43	1.15	0.59 to 2.25
IV/recurrence	93/95	1.21	0.79 to 1.84
Sex			
Male	92/100	1.16	0.78 to 1.73
Female	42/38	0.98	0.45 to 2.13
ECOG PS			
0	49/47	0.80	0.42 to 1.50
1	85/91	1.46	0.95 to 2.25
Smoking			
Never	38/36	1.88	0.80 to 4.40
Smoker	95/100	1.04	0.70 to 1.53
Histology			
Squamous	29/38	0.92	0.49 to 1.72
Adeno	91/86	1.24	0.78 to 1.97
Other	13/12	1.83	0.53 to 6.29
***EGFR* mutation**			
Wild type	56/58	1.09	0.63 to 1.90
Mutated	22/16	2.78	0.66 to 11.67
Unknown	56/64	0.96	0.58 to 1.57
Overall	134/138	1.18	0.83 to 1.69

0.25   0.5   1   2   4   8   16

Favors DP   Favors D

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 $\geq$ 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

AUTHOR CONTRIBUTIONS

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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.

Acknowledgment

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		
	No. of Patients	
Condition	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

Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: a randomized, open-label prospective trial

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Abstract

Purpose Postoperative delirium is the most common postoperative complication in the elderly. The purpose of this study was to evaluate the safety and effectiveness of the preventive administration of low-dose haloperidol on the development of postoperative delirium after abdominal or orthopedic surgery in elderly patients.

Subjects A total of 119 patients aged 75 years or older who underwent elective surgery for digestive or orthopedic disease were included in this study.

Methods Patients were divided into those who did (intervention group, $n = 59$) and did not (control group, $n = 60$) receive 2.5 mg of haloperidol at 18:00 daily for 3 days after surgery; a randomized, open-label prospective study was performed on these groups. The primary endpoint was the incidence of postoperative delirium during the first 7 days after the operation.

Results The incidence of postoperative delirium in all patients was 37.8 %. No side effects involving haloperidol were noted; however, the incidences of postoperative delirium were 42.4 and 33.3 % in the intervention and control groups, respectively, which were not significantly different ($p = 0.309$). No significant effect of the treatment was observed on the severity or persistence of postoperative delirium.

Conclusions The preventive administration of low-dose haloperidol did not induce any adverse events, but also did not significantly decrease the incidence or severity of postoperative delirium or shorten its persistence.

Keywords Haloperidol prophylaxis · Postoperative delirium · Elderly patients · Randomized open-label prospective trial · NEECHAM

Introduction

The incidence of diseases in the elderly requiring surgery, such as femoral neck fractures and colorectal cancer, has

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increased with the aging of the population in Japan [1, 2]. An advanced age is not considered to be a contraindication for surgery worldwide, and surgery is actively performed on patients in their 90 s [3]. However, postoperative management of the elderly is accompanied by many risks. In particular, postoperative delirium, which is the most common postoperative complication [4], represents a major issue in the postoperative treatment of the elderly. It is characterized by a disturbance in consciousness/attentiveness/understanding/cognition and a disorder in the sleep–wake rhythm. It develops suddenly and is likely to vary over the course of a day, inducing various psychiatric symptoms and abnormal behavior [5]. Since postoperative delirium develops in the postoperative recovery phase, it makes postoperative management difficult, disturbs postoperative care and recovery, and is associated with various risks, such as the disturbance of medical care due to the removal of a drip infusion, electrodes and monitors. It also puts an excess burden on medical care workers due to frequent nurse calls and violence, and due to the trauma and fractures caused by tumbles and falls. Moreover, restlessness frequently occurs at night when the nursing staff is shorthanded, which is a serious issue in ward management, and causes excess labor and load on nurses and the patients' families. Postoperative delirium also costs more because it delays the postoperative management and prolongs the hospital stay [6].

Once postoperative delirium develops, only symptomatic treatment with drugs (haloperidol) is currently available, and the effect is insufficient in many cases. A high dose may be necessary, which can markedly influence many patients' physical condition. Therefore, methods to prevent postoperative delirium, to rapidly detect the signs of delirium, to prevent progression to a more severe state and to reduce the persistence of the condition need to be established.

Our previous studies confirmed that the NEECHAM confusion scale (NEECHAM) is useful and objective for the evaluation of postoperative delirium; the incidence of postoperative delirium in 75-year-old or older surgical patients was 55 % when evaluated using the NEECHAM scale. Age, preoperative cognitive dysfunction (a low Mini-Mental State Examination (MMSE) score) and a low preoperative NEECHAM score, but not the surgical department or anesthesia type, were significantly correlated with the development of postoperative delirium, and the incidence of postoperative delirium was higher than 80 % in patients with MMSE and NEECHAM scores lower than 25 and 27 before surgery, respectively, which indicated that these patients represent a high-risk group [7]. We considered that the evaluation of the MMSE and NEECHAM before surgery and the NEECHAM during the postoperative course can facilitate the prevention and early treatment of postoperative delirium in elderly patients.

Pharmacological prevention of postoperative delirium by prophylaxis with antipsychotic medication has been reported in several studies [8]. Oral administration of risperidone and olanzapine reduced the incidence of postoperative delirium in patients undergoing cardiac surgery and hip or knee surgery, respectively [9–11]. However, these drugs are not applicable for many patients, because they are unable to have oral intake for a period of time following surgery. In this respect, either ondansetron or haloperidol, whose intravenous injection has been shown to be effective for the treatment of postoperative delirium [12], can be used. Since the aim of our present study was to incorporate routine drug prophylaxis for surgical patients, ondansetron, whose use is not covered by the health insurance system in Japan, was considered to be unfavorable, leaving haloperidol as the only approved injectable medication that could be used. The effects of haloperidol prophylaxis have already been examined in some studies [13–16], but its efficacy for decreasing the occurrence of postoperative delirium, especially in the elderly, is controversial [13–18].

On the basis of these considerations and the results of our previous studies, we performed a randomized, open-label prospective study to investigate the efficacy and safety of the daily postoperative administration of low-dose haloperidol on postoperative delirium in 75-year-old or older patients who underwent abdominal or orthopedic surgery.

Subjects and methods

Ethical considerations

This study was performed in conformity to the ethical principles based on the Declaration of Helsinki and the 'Ethical Guidelines for Clinical Studies' (notification of the Ministry of Health, Labour and Welfare).

(1) The patients were only included in the study when informed consent was obtained.
(2) The patients' privacy was respected, the secrecy of the recorded results was strictly kept and no information obtained from the study results was used for objectives other than research. To prepare the patient evaluation tables, the patients' privacy protection was sufficiently considered, and patients were identified using identification codes.

Regarding the prophylactic intervention study for postoperative delirium in elderly patients, approval had already been obtained from the Ethics and Conflict of Interest Committee of the National Center for Geriatrics and Gerontology. Other study cooperative institutions started the collection of patients after approval by their respective ethics committee.

Study design and objectives

This was a randomized, open-label prospective trial, and the objective was to evaluate the effect of low-dose haloperidol (2.5 mg/day, for the first 3 days after surgery) on the development, severity and persistence of postoperative delirium, and to evaluate the safety of its preventive intravenous administration to patients 75-year old or older who underwent abdominal or orthopedic surgery.

Patients

The subjects consisted of 121 75-year-old or older patients who underwent elective abdominal surgery under general anesthesia or elective orthopedic surgery under general/spinal anesthesia and gave consent to participate in this study at one of five cooperative institutions (National Center for Geriatrics and Gerontology, Tokyo Metropolitan Geriatric Hospital, Yokohama City University Graduate School of Medicine, Aichi-Saiseikai Hospital and Shizuoka-Saiseikai Hospital) between January 2007 and December 2012. Their age, gender, disease treated with surgery, cognitive function (Mini-Mental State Examination: MMSE [19, 20]), activities of daily living (ADL; Barthel Index [21]), NEECHAM confusion scale (NEE-CHAM) [22–24], and the presence or absence of psychoneurological complications, urinary incontinence, excitement/hyperkinesia during previous hospitalization and the use of psychotropic drugs before admission were evaluated prior to surgery. Patients, who underwent emergency surgery, had a preoperative NEECHAM score below 20, and with periodic dosing with newly added or switched antipsychotics, antidepressants, hypnotics or anti-Parkinson agents within 2 weeks prior to surgery were regarded as ineligible. Patients previously treated with haloperidol for delirium after surgery before the initiation of postoperative preventive haloperidol administration were also excluded.

Measurements and procedures

Eligible patients were enrolled through an internet website on the morning of postoperative day 1 after obtaining consent, and were automatically assigned at that time to the intervention or non-intervention group on a computer using the age, gender and department as adjustment factors.

Haloperidol 0.5A (2.5 mg) was dissolved in 100 ml of saline and intravenously administered by drip infusion once daily at 18:00 from postoperative days 1 to 3 to the intervention group. The dosing time-point of 18:00 was selected because delirium is more likely to occur at night, and also to recover and maintain the sleep–wake rhythm. Regarding the administration method and dose of haloperidol, an intravenous injection of 5–10 mg of haloperidol was recommended as the first-line treatment for orally untreatable delirious patients in the Guidelines for the Treatment of Delirium published by the Japanese Society of General Hospital Psychiatry [25, 26]. The low dose was set in consideration of the physical characteristics of the elderly and the prophylactic nature of the intervention. The duration of administration was decided based on the previous findings in which the development of delirium increased after 24 h, and because severe symptoms continued for approximately 3 days [7]. The development and severity of postoperative delirium were evaluated for 8 days, from postoperative days 0 to 7, using the NEECHAM score.

The NEECHAM score includes the results of an evaluation of three categories: the cognitive information processing function, behavior and physiological control, and the most unfavorable condition over each 24-h period was regarded as the condition on that day. The maximum score of 30 points decreases as the severity of postoperative delirium increases. Patients with a NEECHAM score of 27 or higher, 25–27, 20–24 and 19 or lower were considered to be non-problematic, at high risk of delirium, with mild delirium and with moderate to severe delirium, respectively. This scale has high internal consistency and high reliability regardless of differences among raters, and has been correlated with the Diagnosis and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnostic criteria [27].

The non-intervention group did not receive preventive treatment, and delirium was evaluated in the same way as in the intervention group (Fig. 1).

When delirium developed, conventional treatments, such as the administration of an intravenous antipsychotic drug (such as haloperidol), were administered in both groups.

Assessment and outcomes

Patient data were collected through the internet website, and the identification of personal information was prevented by coding. After completing the data collection from 121 patients, exceeding the planned number of cases, study team members not involved in the medical care of the patients evaluated and analyzed all baseline data and the results. The development and severity of postoperative delirium were evaluated using the NEECHAM score. When the NEECHAM score decreased to below 20 after surgery, the patient was regarded as having developed postoperative delirium.

The primary endpoint was a lower incidence of postoperative delirium in the intervention group than in the non-intervened control group. The secondary endpoints were the severity and persistence of the postoperative delirium in a time-course analysis of the NEECHAM score during the observation period, and the presence or absence of adverse events assumed to be associated with the intervention.

Fig. 1 The study protocol.
NEECHAM NEECHAM
confusion scale, *MMSE* Mini-
Mental State Examination, *ADL*
Activities of daily living
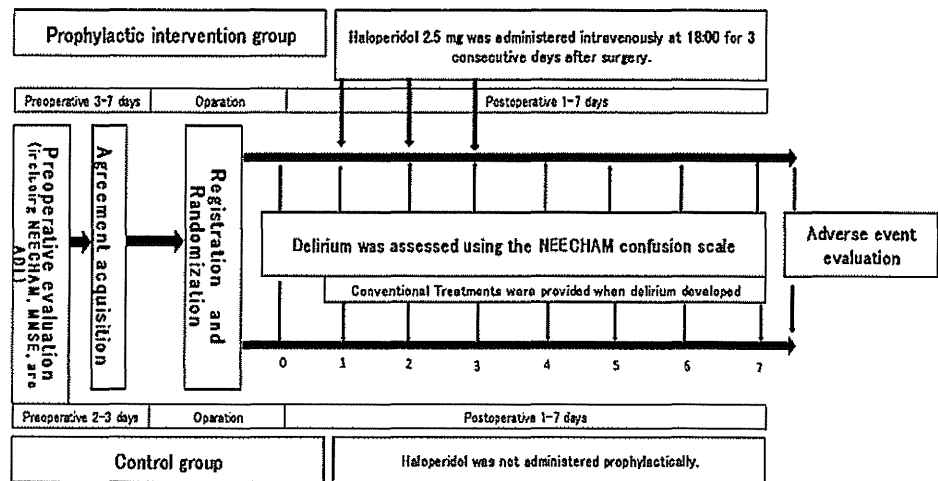
Discontinuation criteria were withdrawal of consent or a change/discontinuation of treatment requested by the patient or her/his legal representative, the development of National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade 2 or more severe adverse events associated with haloperidol, difficulty continuing due to severe physical postoperative complications, and judgment that continuing the trial would be difficult by the physician in charge.

Statistical analysis

Eligible patients were randomly assigned 1:1 to the intervention or non-intervention group by the minimization method according to age ($<75/\geq75$ years), gender (female/male), MMSE score ($<25/\geq25$) and institution. The proportions of patients with severe postoperative delirium, defined as at least one episode of a NEECHAM score <20, were compared between the treatment groups using the Chi-square test. This study was designed to have 80 % power to detect a 25 % difference in the proportion of severe postoperative delirium at a two-sided significance level of 0.05. A multivariate logistic regression including the patient age, gender, MMSE score and the preoperative NEECHAM score as covariates was performed to evaluate the effects of the prophylactic haloperidol treatment after adjustment for potential confounding factors. An odds ratio <1 indicated that the factor was protective against severe postoperative delirium. A supportive analysis using the generalized estimating equation regression model was conducted to compare the incidence of severe delirium between treatment groups during the first 7 days after the operation. The statistical analyses were performed using the SAS software program, version 9.3 (SAS Institute, Cary, NC, USA).

Results

In total, 59 and 62 patients were allocated to the prophylactic intervention and control groups, respectively (121 patients overall). The ages of the intervention and control groups were 80.5 ± 0.5 (mean ± standard deviation) and 80.2 ± 0.5 years, respectively. There were 64 male patients (32 each in the intervention and control groups) and 57 female patients (27 and 30, respectively). Abdominal surgery was performed in 107 patients (52 and 55, respectively); orthopedic surgery in nine patients (five and four) and other surgeries (including vascular surgery) were performed in five patients (two and three patients, respectively, in the intervention and control groups). The preoperative MMSE scores in the intervention and control groups were 23.3 ± 0.7 and 23.0 ± 0.7, and the preoperative Barthel Indices were 85.5 ± 3.1 and 84.0 ± 3.0, respectively, with no significant differences observed between the two groups. The preoperative NEECHAM scores were 27.3 ± 0.4 and 28.1 ± 0.4, respectively, with the intervention group having a slightly lower score, although not significant. No significant differences were noted between the two groups in the presence or absence of urinary incontinence, a past medical history of excitement/hyperkinesia or the preoperative use of oral psychotropic drugs, antidepressants, hypnotics or anti-Parkinson agents. The preoperative baseline data of all patients are shown in Tables 1 and 2.

Postoperative NEECHAM measurements were completed in 119 patients (59 and 60 in the intervention and control groups, respectively) because haloperidol was administered to treat delirium on the day of surgery in two of the 62 patients in the control group (Fig. 2). Postoperative delirium (NEECHAM score lower than 20) developed in 45 patients (37.8 %); 20 (33.3 %; 95 %CI 21.7–46.7 %) and 25 patients (42.4 %; 95 %CI 29.6–55.9 %) in the

Table 1 The baseline data of the patients

Preoperative demographics and characteristics	Prophylactic intervention group (n:59)	Control group (n:62)	p value
Age, mean ± SE	80.5 ± 0.5	80.2 ± 0.5	0.723
Male/female ratio	32/27	32/30	0.773
Type of operation			0.852
Abdominal	52	55	
Orthopedic	5	4	
Other	2	3	
MMSE, mean ± SE	23.3 ± 0.7	23.0 ± 0.7	0.740
NEECHAM score, mean ± SE	27.3 ± 0.4	28.1 ± 0.4	0.133
ADL (Barthel index), mean ± SE	85.6 ± 3.1	84.0 ± 3.0	0.736
Urinary incontinence, yes/no	9/50	8/54	0.710
History of excitement, yes/no	1/58	3/59	0.334
Use of anti-Parkinson agents, yes/no	0/59	1/61	0.327
Use of antipsychotic agents, yes/no	1/58	3/59	0.334
Use of antidepressants, yes/no	4/55	1/61	0.154
Use of hypnotics, yes/no	10/49	7/55	0.371

NEECHAM NEECHAM confusion scale, *MMSE* Mini-Mental State Examination, *ADL* Activities of daily living, *Barthel Index* Representative index of the ADL

Table 2 The underlying diseases and type of surgery

Diseases, surgery	Prophylactic intervention group (n:59)	Control group (n:62)
Abdominal	52	55
Malignancy	36	39
Gastric, gastrectomy/others	11/0	14/2
Colonic, colectomy/others	14/1	14/0
Rectal, LAR/APR/others	2/2/1	4/2/1
Hepatobiliary, hepatectomy/PD/others	1/1/2	1/0/1
Others	1	0
Benign	16	16
Cholelithiasis, cholecystectomy/ choledochotomy	0/4	2/2
Abdominal aortic aneurysm, graft	6	7
Others	6	5
Orthopedic	5	4
Others	2	3

LAR low anterior resection, *APR* abdominoperineal resection, Miles operation, *PD* pancreatoduodenectomy

control and intervention groups, respectively. There was no significant effect on the prevention of postoperative delirium ($p = 0.309$).

The postoperative NEECHAM score showed a pattern similar to that previously reported: the score decreased on postoperative day 1 and then gradually increased and returned to the preoperative level on postoperative days 5–7 [7]. The time-course changes in the mean NEECHAM scores in the control and intervention groups are shown in Fig. 3. The mean postoperative NEECHAM scores on postoperative days 1–7 were lower in the intervention group than in the control group, but no significant differences in the severity or incidence of delirium were noted in the intervention group. The mean durations of the persistence of delirium were 1.10 (95 % CI 0.58–1.62 days) and 1.38 days (95 %CI 0.83–1.95 days) in the control and intervention groups, respectively, with no significant difference between them ($p = 0.356$). The incidences of postoperative delirium were 43.2 % (95 %CI 27.1–60.5 %) and 52.8 % (95 %CI 35.5–69.6 %), when the patients were limited to those with a preoperative MMSE <25, and were 64.3 % (95 %CI 35.1–87.2 %) and 66.7 % (95 %CI 43.0–85.4 %), when limited to those with a preoperative NEECHAM score <27, for the control and intervention groups, respectively, which indicated that no significant effect was noted even when patients were limited to those at high risk for postoperative delirium (preoperative MMSE <25 and preoperative NEECHAM <27; $p = 0.415$ and 0.884, respectively).

When a logistic multivariate analysis was performed that included the presence or absence of the intervention as a parameter (Table 3), the incidence of postoperative delirium was significantly higher in patients at an advanced age with low preoperative MMSE and NEECHAM scores [age: odds ratio = 1.12 (for a 1-year increase in age), $p = 0.043$; preoperative MMSE: odds ratio = 1.15 (for a 1-point decrease in the MMSE score), $p = 0.014$; preoperative NEECHAM: odds ratio = 1.23 (for a 1-point decrease in the NEECHAM score), $p = 0.037$]; however, no significant differences associated with gender or the presence or absence of the intervention were noted ($p = 0.953$ and $p = 0.558$, respectively).

Furthermore, when the analysis was conducted after additionally limiting the subjects to those who underwent abdominal surgery, the odds ratio of the prophylactic administration of haloperidol was 1.25 (95 %CI 0.50–3.12), leading to the same conclusion as expected from our previous work which showed no significant difference in the incidence of postoperative delirium between the patients in the department of surgery and orthopedics [7].

To confirm the reliability of the results of the logistic multivariate analysis, an analysis using the generalized estimating equation was performed. The results are shown