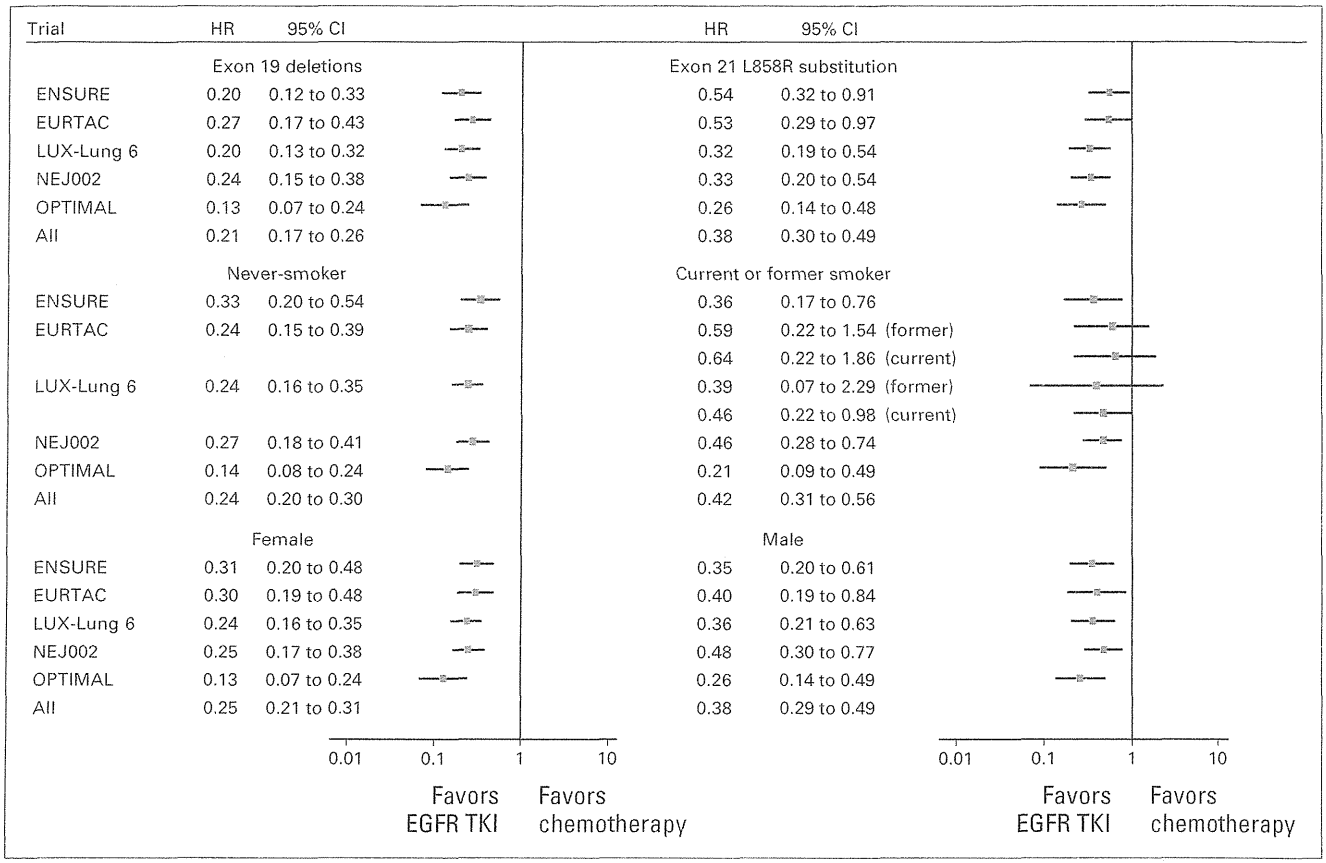

Fig A3. Forest plot of effect of treatment on progression-free survival in subgroups of patients according to different mutations of the epidermal growth factor receptor (*EGFR*), with exclusion of the LUX-Lung 3 and WJTOG 3405 (West Japan Thoracic Oncology Group 3405) trials. HR, hazard ratio; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor.

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Factors associated with a poor response to gefitinib in the NEJ002 study: Smoking and the L858R mutation

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ABSTRACT

Introduction: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) treatment is the standard therapy for non-small cell lung cancer (NSCLC) harbouring EGFR-activating mutations. The NEJ002 phase 3 clinical trial demonstrated the efficacy of EGFR-TKI; gefitinib was significantly superior in both progression-free survival (PFS) and objective response rate (ORR) than carboplatin plus paclitaxel. However, several cases showed no response. In this study, we performed further analysis of the characteristics of these non-responders.
Methods: Available data from NEJ002 on maximum changes in tumour size were obtained from 103 cases (90.4%) and 110 cases (96.5%) in the carboplatin–paclitaxel and gefitinib groups, respectively. Waterfall plots of maximum tumour size changes were created for non-responders.
Results: Five (4.9%) and 9 (8.2%) cases in the carboplatin–paclitaxel and gefitinib groups were non-responders, respectively. The mean pack years of the non-responders in the carboplatin–paclitaxel and gefitinib groups were 0.33 and 31.7, respectively. The ORR of total smokers (61.5%) and heavy smokers (over 40 pack years, 52.6%) in the gefitinib group were significantly lower compared to people who have never smoked (80.0%) ($P = 0.044$ and $P = 0.020$, respectively). Smoker cases also showed a tendency towards lower PFS and overall survival (OS). In addition, the EGFR common mutation types did not affect PFS and OS in gefitinib-treated cases in NEJ002. However, in this study, the ORR and waterfall plots showed that gefitinib-treated non-responders who had a deletion in exon 19 in the EGFR gene exhibited a tendency towards a higher response compared to those with a L858R mutation.
Conclusions: NSCLC patients with a smoking history or the EGFR L858R mutation may demonstrate a poorer response to gefitinib treatment.

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1. Introduction

Lung cancer is the leading cause of cancer death worldwide. Most lung cancer patients are diagnosed in the advanced stages of the disease; thus, despite a significant improvement in the treatment for this malignancy, the prognosis remains poor [1]. Recent studies have demonstrated driver gene mutations, which promote the development of lung cancer [2]. In 2004, epidermal growth factor receptor (EGFR)-activating mutations were discovered in lung cancer by two different groups [3,4]. Subsequently, EGFR-TKI treatment was established as the standard treatment for lung cancer harbouring EGFR mutations based on the results of pivotal trials [5,6].

Currently, the clinically available EGFR-TKIs are gefitinib, erlotinib, and afatinib. In Japan, the North East Japan Study Group (NEJ) demonstrated the efficacy of gefitinib treatment [6]. This study revealed significantly higher objective response rates (ORR) and longer progression-free survival (PFS) of patients with gefitinib treatment compared to patients treated with carboplatin plus paclitaxel, which is the standard cytotoxic chemotherapy (73.7%, 10.8 months vs. 30.7%, 5.4 months, respectively) [6,7]. Although there was no difference in overall survival (OS) (27.7 months for the gefitinib group vs. 26.6 months for the carboplatin plus paclitaxel group), this was assumed to be due to a high crossover rate because gefitinib was administered as a second-line therapy to most patients who received unsuccessful first-line chemotherapy [7]. Smoking history and type of EGFR common mutations (exon 19 deletion or L858R point mutation) did not affect the OS of each treatment group [7].

Gefitinib treatment for EGFR mutation-positive lung cancer demonstrated a significantly higher ORR; however, we observed several cases that showed a poor treatment response. Using data collected from the pivotal NEJ002 study, we analysed the characteristics of these poor response cases or non-responders.

2. Methods

2.1. Patient population

This was a retrospective analysis of clinical data obtained from 230 patients from the NEJ002 study. The eligibility criteria were previously described in the NEJ002 study [6]. Briefly, the criteria included the presence of advanced non-small cell lung cancer (NSCLC) harbouring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M (in which threonine at amino acid 790 was substituted by methionine), no history of chemotherapy, and an age of 75 years or younger. From March 2006 to May 2009, 230 patients were enrolled in the NEJ002 study.

2.2. Study design and treatment

After the exclusion of 2 patients, gefitinib was administered to 114 patients, and the other 114 patients were allocated to receive carboplatin plus paclitaxel. Prior to randomisation, patients were stratified according to sex, clinical stage of NSCLC (IIIB, IV, or postoperative relapse), and institution. Eligible patients were randomly assigned to receive gefitinib (at a dose of 250 mg per day orally) or carboplatin (at a dose equivalent to an area under the concentration–time curve of 6) plus paclitaxel (at a dose of 200 mg per square metre of body surface area). Gefitinib was administered until disease progression, development of intolerable toxic effects, or withdrawal of consent. Carboplatin plus paclitaxel were both administered on the first day of every 3-week cycle for at least three cycles. Retrospective analysis was performed using the currently available data. The available data on maximum changes in the tumour target lesion size from baseline were evaluated in 103 patients (90.4%) and 110 patients (96.5%) in the carboplatin plus paclitaxel and gefitinib groups, respectively. Seven patients in the carboplatin plus pactlitaxel group and 1 patient in the gefitinib group could not be evaluated for treatment response [6]. The remaining 4 patients in the carboplatin plus paclitaxel group and 3 patients in the gefitinib group showed that the tumour progression after each treatment made the tumour-target-lesion immeasurable. Progression of atelectasis or increased pleural effusion occurred in most of the cases.

2.3. Clinical assessments

An assessment of the maximum changes in tumour size was performed using data for the evaluation of ORR with computed tomography (CT) every 2 months. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria In Solid Tumours (RECIST, version 1.0). We defined a non-responder as a patient whose tumour-target-lesion size showed no change or increased despite the administration of each treatment during complete first-line treatment. Treatment response and PFS were determined by an external review of the CT scans by experts who were blinded to the treatment assignments. OS was evaluated for the period from the date of randomisation to the date of death.

2.4. Statistical analysis

The smoking pack years between two the groups were compared using the Wilcoxon rank sum test. The ORR was compared using Fisher's exact test. Kaplan–Meier survival curves were drawn for PFS and OS and were compared using the log-rank test. Each analysis was performed using a two-sided, 5% significance level and a 95% confidence interval using SAS for Windows software (release 9.1.3, SAS Institute, Cary, NC).

3. Results

3.1. Fourteen cases showed no response to either treatment

Waterfall plots showing maximum changes in the tumour target lesion size from baseline are indicated in Fig. 1A (lower). As previously demonstrated in the NEJ002 study, in which gefitinib treatment showed a higher response rate than carboplatin–paclitaxel treatment, the gefitinib group had more cases that showed a partial and complete response to the treatment compared to the carboplatin–paclitaxel group. However, 5 patients (4.9%) in the carboplatin–paclitaxel group and 9 patients (8.2%) in the gefitinib group showed no response and instead experienced no decrease in tumour size or an increased tumour size (Table 1). We analysed the characteristics of these non-responder cases for specific predictive factors of response to treatment.

3.2. Non-responders to gefitinib treatment showed a tendency towards higher smoking pack years than the carboplatin plus paclitaxel group

The number of smoking pack years of each case is indicated in Fig. 1A (upper). When only non-responders were evaluated, those in the gefitinib treatment group showed a tendency towards higher smoking pack years. The mean pack years of cigarette smoking of the non-responders in the carboplatin plus paclitaxel and gefitinib groups were 0.3 and 31.7, respectively ($P = 0.164$. Fig. 1B).

Among the 9 non-responders of the gefitinib treatment group, 4 of the subjects were never smokers (Table 1). Case GC-007 showed a long duration of stable disease, which indicated the partial efficacy of gefitinib. Case GC-054 had an exon 18 minor mutation in

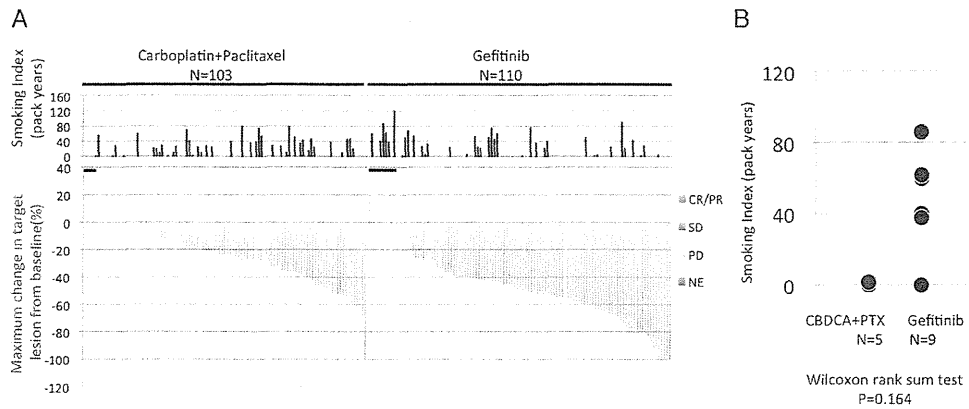

Fig. 1. (A) Lower: maximum changes in the target lesion size from the baseline of each case in the NEJ002 study were demonstrated using waterfall plots. The black line indicates the cases with an equivalent or increased tumour size as non-responders. Upper: smoking pack years of each case. (B) Smoking pack years of non-responder cases of each treatment group.

the EGFR gene. Our group previously published data on the poor treatment response to gefitinib in patients with minor mutations [8]. Both case GC-194 and case GC-063 discontinued gefitinib treatment due to serious adverse event, including drug-induced lung disease and liver dysfunction, respectively. In contrast, among the remaining 5 patients who had a smoking history, only 1 patient had an exon 18 minor mutation, and the other patients had no episodes of serious adverse events. In the carboplatin plus paclitaxel group, only 1 patient ceased the first-line treatment due to the onset of ileus, and the remaining non-responders did not show any specific clinical characteristics.

3.3. PFS and OS of the gefitinib-treated smoker group showed a tendency towards poor prognosis

The ORR of the gefitinib group was 73.7% [6]. When divided into 2 groups by smoking history, the ORR of the smoker group was significantly lower than the never smoker group (61.5% vs. 80.0%, $P=0.044$, Table 2). Moreover, the ORR of the heavy smoker group (over 40 pack years) was 52.6% and significantly lower than the non-smoker group ($P=0.020$).

Kaplan–Meier curves of the PFS and OS are shown in Fig. 2A and B. Although not statistically significant, the smoker cases showed a tendency towards lower PFS and OS compared to the non-smoker cases ($P=0.074$ and $P=0.164$, respectively).

3.4. NSCLC patients with the EGFR L858R mutation showed a relatively poor response to gefitinib compared to patients with an exon 19 deletion mutation

Although we previously reported the PFS and OS of the gefitinib treated exon 19 deletion mutant group did not show any difference compared to the L858R mutation group [6,7], the types of EGFR mutations may also be an important predictive factor of the treatment response, as shown in Table 1, which depicts the non-responders' EGFR mutation status. Namely, three non-responders (GC-007, 011, 194) with gefitinib treatment, who showed increases of over 20% in tumour growth from baseline, had a L858R mutation. A comparison of the patients based on EGFR common activating mutations, L858R and exon 19 deletion, revealed that ORR (Table 3) and the maximum tumour size changed from baseline (Fig. 3A and B) in gefitinib-treated patients and indicated that the L858R mutation was worse than an exon 19 deletion mutation. In contrast, patients who received carboplatin plus paclitaxel did not show any differences.

Table 1
Individual non-responders cases from NEJ002. Non-responder denotes patients who never had decrease in the size of measurable lesion during first-line treatment.

Case No.	Maximum change[a]	Sex	Age	ECOG-PS	Histology	Stage	EGFR mutation	Smoking pack years	Response	Duration[b]	OS (month)
Carboplatin + paclitaxel											
GC-068	+9.7	Female	72	1	AD	IV	Exon 19 deletion	0	PD	0.9	43.7
GC-176	+2.7	Female	69	1	AD	IV	Exon 19 deletion	0	SD	1.6	25.6
GC-001	0	Female	72	1	AD	IV	G719S	0	SD	1.9	9.8
GC-077	0	Male	71	1	AD	IV	Exon 19 deletion	0	SD	1.7	16.4
GC-220	0	Male	75	1	AD	IV	Exon 19 deletion	1.65	NE	0.8	20.6
Gefitinib											
GC-007	+33.3	Female	70	1	AD	IIIB	L858R	0	SD	22.0	53.6
GC-011	+32.1	Male	56	1	AD	Relapse	L858R	60	PD	2.3	21.9
GC-194	+22.2	Female	60	1	AD	IV	L858R	0	PD	1.1	1.7
GC-054	+21.1	Male	68	1	AD	IV	G719C	0	PD	1.9	11.8
GC-158	+8.8	Male	65	0	AD	IV	Exon 19 deletion	40	SD	2.3	27.6
GC-183	+7.8	Male	63	0	AD	IIIB	Exon 18	86	PD	2.2	5.7
GC-195	+7.6	Male	51	1	AD	IV	Exon 19 deletion	62	PD	2.0	10.9
GC-031	+2.4	Male	64	1	AD	IV	Exon 19 deletion	37.5	PD	0.3	10.8
GC-063	0	Female	67	0	AD-SQC	IIIB	Exon 19 deletion	0	SD	1.2	37.1

AD: adenocarcinoma; AD-SQC: adenosquamous carcinoma; PD: progressive disease; SD: stable disease; NE: not evaluated.
[a] Maximum change from baseline during the first-line treatment (%).
[b] Duration from entry to maximum size (month).

Table 2
Response of cases categorised by smoking history in the gefitinib treatment group.

Gefitinib Treatment Group	Non Smoker	Smoker Total	Light Smoker Under 40 pack years	Heavy Smoker Over 40 pack years
Total	75 (100.0%)	39 (100.0%)	20 (100.0%)	19 (100.0%)
CR	5 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	55 (73.3%)	24 (61.5%)	14 (70.0%)	10 (52.6%)
SD	9 (12.0%)	9 (23.1%)	5 (25.0%)	4 (21.1%)
PD	6 (8.0%)	5 (12.8%)	1 (5.0%)	4 (21.1%)
NE	0 (0.0%)	1 (2.6%)	0 (0.0%)	1 (5.3%)
CR + PR	60 (80.0%)	24 (61.5%)	14 (70.0%)	10 (52.6%)
95%CI	(69.2%, 88.4%)	(44.6%, 76.6%)	(45.7%, 88.1%)	(28.9%, 75.6%)
	P=0.044			
	P=0.020			
Fisher's exact test				

CR: complete response; PR: partial response; PD: progressive disease; SD: stable disease; NE: not evaluated.

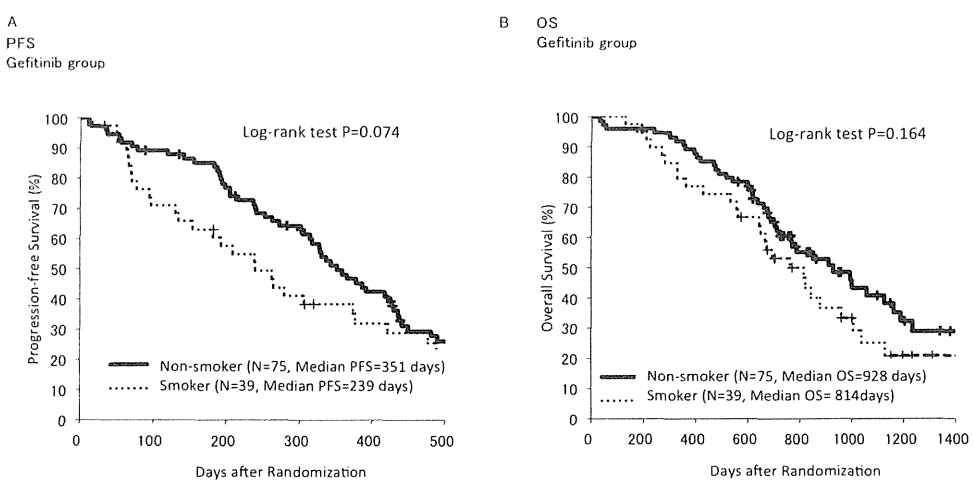

Fig. 2. The survival curves of non-smokers and smokers in the gefitinib treatment group of the NEJ002 study, as described by the Kaplan–Meier method and compared using the log-rank test. (A) PFS. (B) OS.

4. Discussion

For NSCLC cases with an EGFR mutation, gefitinib treatment increased both the ORR and PFS more than carboplatin plus paclitaxel treatment. Nevertheless, the number of non-responders to gefitinib treatment was also higher compared to patients treated with carboplatin plus paclitaxel, 9 (8.1%) vs. 5 (4.4%), respectively. Interestingly, non-responders of the gefitinib group, who had neither a serious adverse event nor minor EGFR mutations, had a smoking history. This result indicates that a smoking history may be an important predictive factor for gefitinib treatment. The type of EGFR-activating mutation may also be another predictive factor for the response to gefitinib treatment; NSCLC patients with a L858R mutation exhibited a poorer response to gefitinib compared to patients with an exon 19 deletion mutation.

Most of the EGFR-mutant patients who had a smoking history or L858R mutation showed a better response to gefitinib compared to carboplatin plus paclitaxel. However, the response rate was significantly lower, particularly in the heavy smoker group compared to the non-smoker group.

Several studies indicated that NSCLC patients harbouring EGFR mutations with many smoking pack years showed a relatively poor response to EGFR-TKI treatment [9–11]. Several mechanisms have been proposed to explain the poorer response to EGFR-TKI in patients with a smoking history. One group found that cigarette smoking induced EGFR posttranslational changes [12] and that the Src oncogene may confer resistance to treatment [13]. Another group demonstrated that activation of the nicotinic acetylcholine receptor by cigarette smoking induced EGFR-TKI resistance [14]. Furthermore, many chemicals contained in cigarette smoke have a high activity of mutagenesis [15]. Consistent with this finding, the rate of gene alteration in smoker patients with NSCLC harbouring EGFR mutations was considerably higher compared to non-smokers [16,17]. Moreover, lung cancer cells derived from lung

Table 3
Response of cases categorised by the types of EGFR common mutation.

	Gefitinib		Carboplatin+paclitaxel	
	L858R	exon 19 deletion	L858R	exon 19 deletion
Total	49 (100.0%)	58 (100.0%)	48 (100.0%)	59 (100.0%)
CR	1 (2.0%)	4 (6.9%)	0 (0.0%)	0 (0.0%)
PR	32 (65.3%)	44 (75.9%)	15 (31.3%)	18 (30.5%)
SD	11 (22.4%)	6 (10.3%)	23 (47.9%)	28 (47.5%)
PD	4 (8.2%)	4 (6.9%)	8 (16.7%)	8 (13.6%)
NE	1 (2.0%)	0 (0.0%)	2 (4.2%)	5 (8.5%)
CR + PR	33 (67.3%)	48 (82.8%)	15 (31.3%)	18 (30.5%)
95%CI	(52.5%, 80.1%)	(70.6%, 91.4%)	(18.7%, 46.3%)	(19.2%, 43.9%)
Fisher's exact test	P=0.074		P=1.000	

CR: complete response; PR: partial response; PD: progressive disease; SD: stable disease; NE: not evaluated.

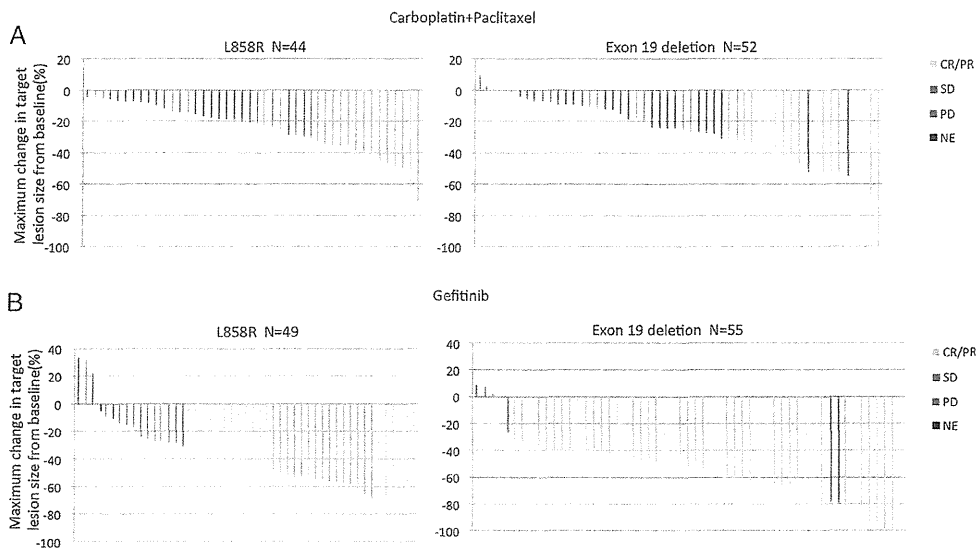

Fig. 3. Maximum changes in the target lesion size from the baseline of each case in the carboplatin plus paclitaxel (A) and gefitinib (B) groups. The patients were categorised into 2 groups according to the type of EGFR common mutation, L858R and exon 19 deletion.

of heavy smokers contained "driver" EGFR mutations and many other "passenger" gene mutations. These passenger genes may modify signal transduction pathways that render cell death more difficult to be induced by treatment with EGFR-TKI alone.

Recently, treatment of other clinically available EGFR-TKI, such as erlotinib and afatinib, in NSCLC patients with an exon 19 deletion showed a higher response than those with the L858R mutation [18,19]. However, for gefitinib phase 3 studies, the type of EGFR mutation did not affect PFS and OS [5–7]. In the present study, we found that gefitinib treatment also showed a tendency towards a favourable response in patients with an exon 19 deletion mutation based on an evaluation of short-term responses, such as ORR and the maximum change in tumour size from baseline. If the response of gefitinib treatment was affected by EGFR subtypes, then all three EGFR-TKIs demonstrated a higher treatment response in patients with an exon 19 deletion compared to those with the L858R mutation to varying degrees. There was no difference in the half maximal inhibitory concentration (IC_{50}) of gefitinib given to cancer cell lines harbouring an exon 19 deletion and those with the L858R mutation [20,21]. However, a recent study revealed that the crystal structure of the L858R mutation is more stable in maintaining the active form than the exon 19 deletion mutation [22]. The rationale underlying these differences in response to EGFR-TKI may be explained by their activating mechanism.

In this study, we found candidate predictive factors of the response to gefitinib treatment. Due to the high efficacy of gefitinib treatment, the number of non-responders was very small. To confirm the results of this study, additional data on non-responders to EGFR-TKI treatment should be collected for further analysis.

5. Conclusion

In this study, on the basis of the characteristics of non-responders to gefitinib in the NEJ002 study, we found two potential factors for a poor response to EGFR-TKI treatment. Patients who had a smoking history showed a significantly lower response rate to gefitinib treatment. Gefitinib treatment may be more effective in patients with an exon 19 deletion than those with the L858R mutation. To clarify these relationships, further studies using additional data on non-responders are needed.

Conflict of interest

Dr. Maemondo, Dr. Inoue, Dr. Oizumi, Dr. Gemma, Dr. Hagiwara, and Dr. Nukiwa received a lecture fee from Astrazeneca Pharmaceutical for this work that is under consideration for publication. Dr. Maemondo participated on the advisory board. Dr. Kinoshita, Dr. Saijo, and Dr. Morita received a lecture fee from Astrazeneca Pharmaceutical for other work. All of the remaining authors have declared no conflicts of interest.

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Original article

Phase II study of amrubicin combined with carboplatin for refractory relapsed small-cell lung cancer: North Japan Lung Cancer Group Trial 0802

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ABSTRACT

Background: Amrubicin (AMR), a new anthracycline agent, has shown promising results for advanced small-cell lung cancer (SCLC), although the efficacy of AMR alone against refractory relapsed SCLC is insufficient. This study was conducted to evaluate the safety and efficacy of the combination of AMR and carboplatin (CBDCA) in patients with refractory relapsed SCLC.

Methods: Patients with advanced SCLC who relapsed within 90 days after the completion of first-line chemotherapy received AMR (30 mg/m^2, days 1–3) and CBDCA (area under the curve 4.0 mg mL^{-1} min^{-1}, day 1) every 3 weeks. The primary endpoint of this study was the overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS), overall survival, and the toxicity profile. Assuming that an ORR of 45% in eligible patients would indicate potential usefulness and an ORR of 20% would be the lower limit of interest, with $\alpha=0.10$ and $\beta=0.10$, at least 24 patients were required.

Results: Among 29 eligible patients, the ORR was 34% (90% confidence interval, 20–48). The median PFS was 3.5 months, whereas the median survival time was 7.3 months. The most common grade 3–4 toxicity was neutropenia (79%), although only one patient (3%) suffered from febrile neutropenia. Non-hematological toxicities were of moderate severity and no treatment-related death was observed.

Conclusions: This is the first prospective study of AMR combined with CBDCA for refractory relapsed SCLC, which was effective and well tolerated. However, further investigation of this regimen is warranted.

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1. Introduction

Lung cancer is currently the leading cause of cancer death in many countries, and small-cell lung cancer (SCLC) accounts for 12–15% of all lung cancer cases [1]. SCLC is chemosensitive, and the standard first-line chemotherapy for advanced SCLC is platinum-doublet regimens such as cisplatin (CDDP) plus etoposide (ETP) or CDDP plus irinotecan (CPT) [2,3]. Despite high response rates to first-line chemotherapy, most patients experience SCLC relapse. The efficacy of second-line chemotherapy differ according to the relapse type (sensitive relapse, defined as relapse after >90 days from the completion of first-line chemotherapy or refractory relapse, defined as relapse during first-line chemotherapy or within 90 days after completion of first-line chemotherapy). There has been no standard treatment for patients with refractory relapsed SCLC, and few single agents have shown a response rate of >10% [4].

Amrubicin (AMR), a new anthracycline agent, has shown some promising results for advanced SCLC. A Japanese phase II study of the intravenous administration of single-agent first-line AMR therapy (45 mg/m^2) for 3 consecutive days demonstrated a high overall response rate (ORR) (75.8%) and long median survival time (MST) (11.7 months) [5]. AMR was also more effective than topotecan (TOP) for chemosensitive relapsed SCLC in our previous phase II trial (response rates, 38% and 13%, respectively), although the response rate of AMR for refractory relapsed SCLC was only 17% (that of TOP was 0%) [6], a finding compatible with the result of AMR in a similar population in a subsequent large phase II study by Ettinger [7].

Since some of the patients with refractory relapsed SCLC did not receive a sufficient dose of platinum agent during first-line chemotherapy, we thought that second-line chemotherapy consisting of AMR combined with platinum might be worth investigating. Thus, we conducted this phase II study to evaluate the safety and efficacy of the combination of AMR and CBDCA in patients with refractory relapsed SCLC.

2. Patients and methods

2.1. Patient selection

This multicenter phase II trial was conducted in accordance with the principles outlined in the Helsinki Declaration of the World Medical Association, and the protocol was approved by the institutional review board of each participating institution (Approval date: December 15, 2008; Approved No: 2008-365). Patients >20 years of age with histologically or cytologically confirmed SCLC who had progressed during first-line chemotherapy or had relapsed within 90 days after the completion of first-line chemotherapy were enrolled in this study. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status (PS) of 0–2, measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST), an estimated life expectancy ≥3 months, and adequate organ function (white blood cell count ≥4000/mm^3, absolute neutrophil count ≥2000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.0 g/dL, serum bilirubin ≤1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, creatinine level ≤1.5 mg/dL, and arterial oxygen pressure ≥60 mmHg). Written informed consent was obtained from all enrolled patients. Patients with symptomatic brain metastasis, interstitial lung disease, massive effusion requiring drainage, or severe comorbidities such as uncontrolled diabetes or cardiac disease were excluded. This trial was registered at UMIN (ID: R000001597).

2.2. Treatment schedule

The AMR was diluted in 50 mL of normal saline and administered by 10-min intravenous infusion at a dose of 30 mg/m^2 on days 1–3 of each treatment cycle. CBDCA was diluted in 250 mL of 5% glucose solution or normal saline and administered at infusion intervals of ≥30 min at a dose of area under the curve (AUC) 4.0 mg mL^{-1} min^{-1} after AMR on day 1. The doses of both agents were determined according to our previous phase I study of this combination for patients with untreated SCLC [8]. The treatment was repeated every 21 days. Premedication with corticosteroids and an antiemetic 5-HT$_3$ antagonist was recommended. The dose of AMR was reduced by 5 mg/m^2 each in the subsequent cycle in cases of severe toxic effects such as grade 3 or more non-hematological toxicities, thrombocytopenia ≤20,000/mm^3, grade 4 neutropenia lasting ≥4 days, or febrile neutropenia in the previous cycle. Use of granulocyte colony-stimulating factor (G-CSF) was permitted for neutropenia but not for prophylaxis. No prophylactic antibiotic support was planned. All patients were scheduled to receive at least three cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician

decided to discontinue the treatment. Subsequent chemotherapy after disease progression was not limited.

2.3. *Patient assessment*

Patient assessments, including a physical examination, a complete blood count, and biochemistry analysis, were repeated once a week after the initial evaluation. Tumor measurement was performed during the baseline assessment by computed tomography (CT) and was repeated every month until the best response to the protocol treatment was identified. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined based on RECIST version 1.0. CR and PR were confirmed by re-assessment performed at least 4 weeks after the first observation. SD was confirmed by re-assessment performed at least 6 weeks after registration. After confirmation, CT scans were acquired every 2 months until PD was observed. The CT scans of all patients were extramurally reviewed to confirm the response and progression-free survival (PFS). PFS was defined as the time from the date of registration to the date of the first observation of PD or death. Overall survival (OS) was defined as the time from the date of registration to the date of death or the latest follow-up (censored case). Toxicities were evaluated according to Common Terminology Criteria for Adverse Events version 3.0.

2.4. *Statistical analysis*

The primary endpoint of this study was the overall response rate (ORR), and secondary endpoints were PFS, OS, and the toxicity profile. Assuming that an ORR of 45% in eligible patients would indicate potential usefulness while an ORR of 20% would be the lower limit of interest, with α=0.10 and β=0.10, at least 24 patients were required. Survival estimation was performed using the Kaplan–Meier method.

3. Results

3.1. *Patient characteristics and treatment delivery*

Between September 2008 and May 2011, 30 patients were enrolled from 10 institutions. One patient was excluded because of ineligible histology. Most of patients were male with a good PS (Table 1). Most patients received a CBDCA-based regimen as first-line chemotherapy, with a median of 4 cycles (range, 2–11 cycles). The median number of treatment cycles in the current study was 4 (range, 1–7), and 83% (24 of 29) of patients received three or more cycles.

3.2. *Efficacy*

All 29 patients were evaluable for response. The ORR was 34% (90% confidence interval, 20–48) and the disease-control rate was 83% (Table 2). The response rate of patients treated with CBDCA-based first-line chemotherapy was 40%, whereas that of patients treated with CDDP-based first-line chemotherapy was 22%, although the difference was not statistically significant. The response rates of patients treated with ETP and of those treated with CPT as first-line chemotherapy were 35% and 33%, respectively. At the data cut-off point in September 2013, the median PFS was 3.5 months and the median survival time was 7.3 months (Fig. 1).

Table 1 – Patient characteristics.

Number of patients	29
Gender	
Male	26
Female	3
Age (years)	
Median	67
Range	50–81
Performance status	
0	9
1	16
2	4
Prior chemotherapy	
Cisplatin+etoposide	2
Carboplatin+etoposide	15
Cisplatin+irinotecan	7
Carboplatin+irinotecan	5

Table 2 – Response.

Response	Number of patients	%	90% CI
Complete response	0	0	
Partial response	10	34	
Stable disease	14	48	
Progressive disease	5	17	
Overall response rate	10	34	20–48
Disease control rate	24	83	

CI, confidence interval.

3.3. *Safety*

The toxicities (>grade 2) are summarized in Table 3. The most common adverse event in this study was neutropenia (79%), although only one patient (3%) suffered from febrile neutropenia. Thirteen patients (45%) required G-CSF support, the median duration of which was 4 days (range, 1–11). Two patients (7%) received a blood transfusion. Eight patients (28%) required AMR dose reduction due to hematological toxicity. Non-hematological toxicities were moderate. One patient died only 5 days after the initiation of protocol treatment. The attending physician reported that the cause of death was rapid progression of SCLC, and the independent data and safety monitoring committee of this study reviewed the clinical course and accepted the physician's decision. No treatment-related death was observed.

4. Discussion

This study met its primary endpoint. Since there have been few promising monotherapy options for refractory relapsed

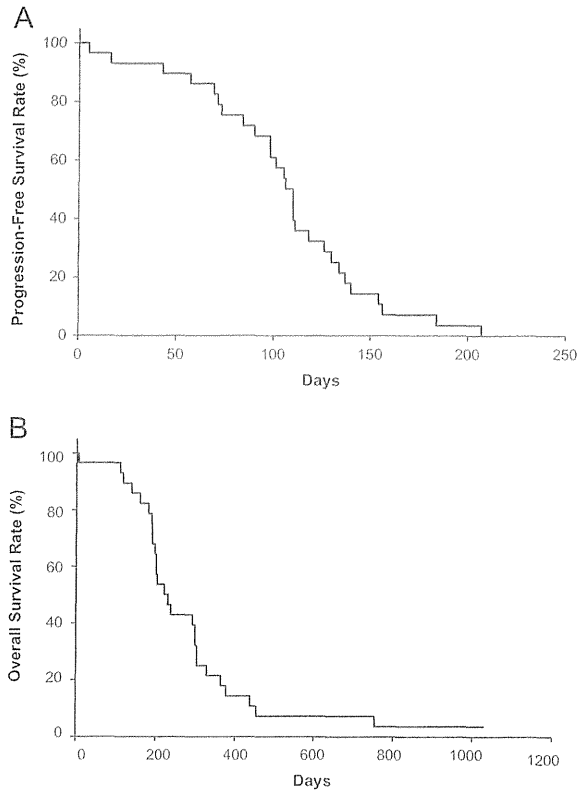

Fig. 1 – (A) Progression-free survival and (B) overall survival.

Table 3 – Toxicity profile.

Toxicity (≥ grade 2)	Grade (CTCAE)			
	Number of patients			
	2	3	4	Grade 3/4 (%)
Hematological				
Neutropenia	0	10	13	23 (79%)
Decreased hemoglobin	11	6	1	7 (24%)
Thrombocytopenia	6	4	3	7 (24%)
Febrile neutropenia	–	1	0	1 (3%)
Non-hematological				
Infection	4	2	0	2 (6%)
Nausea	2	0	0	0
Fatigue	1	0	0	0
Mucositis oral	1	0	0	1 (3%)
Stomach pain	1	0	0	0
Phlebitis	1	0	0	0
Hiccups	1	0	0	0
Pain	1	0	0	0
Interstitial lung disease	0	1	0	1 (3%)
Hyponatremia	0	2	0	2 (6%)
Hypoglycemia	0	0	1	1 (3%)

CTCAE, Common terminology criteria for adverse events.

SCLC, the combination of AMR and CBDCA is worth investigating. Contrary to our expectations, most patients in this study received sufficient cycles of platinum-doublet therapy as first-line chemotherapy. The ORR might have increased if more patients had been treated with insufficient first-line chemotherapy. According to subgroup analysis, this regimen might be suitable for patients treated with CBDCA as first-line chemotherapy. The efficacy of CBDCA plus AMR was not different in patients treated with ETP or CPT as first-line chemotherapy with platinum, which was consistent with our previous result of AMR as second-line chemotherapy [6]. Although the sample size was too small, the above-mentioned results require further validation.

In another Japanese study, even AMR alone demonstrated a quite high response rate (40%) in refractory relapsed SCLC [9], although the result might be biased due to its small sample size ($n=16$), considering the result of a subsequent larger study [7]. Other studies have used combined regimens for relapsed SCLC, some of which suggested high efficacy. However, most of those studies included both sensitive and refractory relapse patterns [4]; thus, their usefulness in refractory relapsed SCLC was unclear.

Toxicity is another important issue for such combination regimens. The above-mentioned previous regimens for relapsed SCLC were generally very toxic. For example, Kubota reported that dose-intensive CODE (CDDP, vincristine, doxorubicin, and ETP) could result in an ORR of approximately 80% in patients with refractory relapsed SCLC; however, that regimen required prophylactic G-CSF support due to severe neutropenia [10]. In contrast, AMR combined with CBDCA showed moderate toxicity in this study, which might be attributable to the dose of CBDCA being AUC 4. We reported this regimen in another study, where toxicity profiles tended to be similar and the efficacy for SCLC was sufficient (ORR was 89% as first-line treatment) [11]. Regarding the AMR dose, the current dose was one level lower than the recommended dose in our phase I and phase II studies of patients with chemotherapy-naïve SCLC because we considered that previously treated patients would be at a higher risk of myelosuppression. Although we believe this combination with the current dosage would be worth investigating in the second-line setting in terms of the risk–benefit balance, there might be scope for increasing the AMR dose to increase its efficacy.

This study has a few limitations. First, the sample size was too small to draw definite conclusions, the efficacy of this combination needs to be confirmed in a future phase III study in which the current regimen could be compared with AMR alone. Second, the drug dose might be insufficient for refractory relapsed cases. Considering that the toxicity of the current dose was moderate, there might be scope to increase the CBDCA or AMR dosage. In addition, the patients that would benefit most from the re-administration of platinum during second-line chemotherapy should be identified.

In conclusion, AMR combined with CBDCA was effective for refractory relapsed SCLC and demonstrated acceptable toxicity. Since treatment options for patients with refractory relapsed SCLC remain limited, further investigation of this regimen is warranted.

Conflict of interest

Akira Inoue received honoraria and research funding from AstraZeneca; Satoshi Oizumi received honoraria from AstraZeneca and research funding from Eli Lilly; Toshihiro Nukiwa received honoraria from Boehringer Ingelheim.

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Clinical Trial Results

Randomized Phase II Trial Comparing Carboplatin Plus Weekly Paclitaxel and Docetaxel Alone in Elderly Patients With Advanced Non-Small Cell Lung Cancer: North Japan Lung Cancer Group Trial 0801

Makoto Maemondo,[a] Akira Inoue,[b] Shunichi Sugawara,[c] Toshiyuki Harada,[d] Yuji Minegishi,[e] Kazuhiro Usui,[f] Koji Miwa,[g] Naoto Morikawa,[h] Mariko Kambe,[i] Kenji Ube,[j] Kana Watanabe,[a] Osamu Ishimoto,[c] Tomohiro Sakakibara,[b] Akihiko Gemma,[e] Toshihiro Nukiwa[k]

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Author Summary

Abstract

Background. Standard first-line chemotherapy for elderly non-small cell lung cancer (NSCLC) patients has been monotherapy with vinorelbine or gemcitabine. Docetaxel has also been considered as an alternative option for the elderly population in Japan. We have previously demonstrated the high efficacy of carboplatin plus weekly paclitaxel for elderly NSCLC patients. Consequently, we conducted a randomized phase II study to select the proper regimen for a future phase III trial.

Methods. Eligible patients were aged 70 years or older with newly diagnosed advanced NSCLC. Patients were randomly assigned either to a combination of carboplatin (area under the curve: 6 mg/mL per minute) with weekly paclitaxel (70 mg/m^2) (CP regimen) or to single-agent docetaxel (60 mg/m^2). The primary endpoint of this study was objective response rate. Secondary endpoints were progression-free survival, overall survival, and toxicity profile.

Results. Among 83 eligible patients (41 to CP, 42 to docetaxel), the objective response rates were 54% (95% confidence interval: 39%–69%) and 24% (95% confidence interval: 11%–37%) and median progression-free survival was 6.6 months and 3.5 months in the CP arm and the docetaxel arm, respectively. Severe neutropenia, febrile neutropenia, and nausea were significantly frequent in the docetaxel arm, whereas toxicities in the CP arm were generally moderate. One treatment-related death was observed in the docetaxel arm.

Conclusion. The CP regimen achieved higher activity with less toxicity than single-agent docetaxel. Considering the results of this phase II trial and the IFCT-0501 trial, we have selected the CP regimen for a future phase III trial in elderly patients with advanced NSCLC. ***The Oncologist*** 2014;19:352–353

Discussion

The objective response rate (ORR) of carboplatin (area under the plasma curve: 6 mg/mL per minute) with weekly paclitaxel (70 mg/m^2) (CP regimen) met the primary endpoint of this study, achieving a higher response rate than single-agent docetaxel in this population of elderly patients with non-small cell lung cancer (NSCLC) (Fig. 1). In addition, the CP regimen achieved longer progression-free survival with less toxicity excluding moderate anemia and thrombocytopenia in comparison with docetaxel. Consequently, we have selected the CP regimen as a candidate for a future phase III trial.

Although monotherapy with third-generation agents has been regarded as the preferred treatment option for elderly patients with NSCLC [1–6], Quoix et al. recently reported the results of IFCT-0501, a phase III study comparing a similar CP regimen (carboplatin [area under the plasma curve: 6 mg/mL per minute] plus weekly paclitaxel at 90 mg/m^2) with monotherapy with either vinorelbine or gemcitabine in an elderly population [7]. IFCT-0501 demonstrated significant superiority to the CP regimen in terms of the efficacy (ORR and overall survival); however, severe toxicity in the CP arm, including a treatment-related death (TRD) rate of 4.4%, was of concern. The dose of paclitaxel in the current study was 70 mg/m^2, and this could explain the lower toxicity of CP. No TRDs have been

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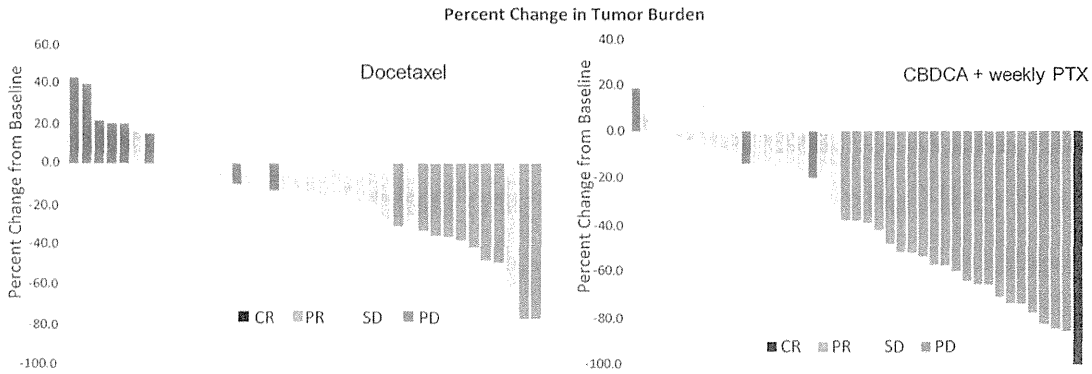

Figure 1. Waterfall plots of the docetaxel arm and the CP arm in this study.

Abbreviations: CBDCA, carboplatin; CP, carboplatin with weekly paclitaxel; CR, complete response, PD, progressive disease; PR, partial response; PTX, paclitaxel; SD, stable disease.

observed in the CP arm of this study or in our previous study using the same regimen.

Regarding the efficacy of CP, the ORR and progression-free survival in this study (54% and 6.6 months) are consistent with results achieved with the same regimen in our previous study (55% and 6.0 months) [8]. Because the evaluation of response in this study was performed by centralized review blinded as to the treatment, we believe the results were not biased. Furthermore, the ORR of the docetaxel arm in this study (24%) was quite consistent with previous results achieved with docetaxel in Japanese phase III trials with elderly NSCLC patients (23% in WJTOG9904 and 25% in JCOG0802) [6, 9]. Importantly, the rate of febrile neutropenia, an independent and poor prognostic factor in elderly NSCLC patients receiving chemotherapy, has been consistently high (>10%) in the docetaxel arm in the current study and in previous Japanese studies. In addition, one TRD was observed in the docetaxel arm in this study. All of these observations suggest that monotherapy with docetaxel might be more toxic than CP for elderly patients.

Author disclosures and references available online.