Carboplatin plus Either Docetaxel or Paclitaxel for Japanese Patients with Advanced Non-small Cell Lung Cancer

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Abstract. *Aim: Assessment of the efficacy of docetaxel plus carboplatin vs. paclitaxel plus carboplatin in Japanese patients with advanced non-small cell lung cancer (NSCLC). Patients and Methods: Chemotherapy-naïve patients were randomly assigned at a ratio of 2 to 1 to receive six cycles of either docetaxel (60 mg/m^2) plus carboplatin [area under the curve (AUC)=6 mg/ml min] or paclitaxel (200 mg/m^2) plus carboplatin (same dose), on day 1 every 21 days. The primary end-point was progression-free survival (PFS). Results: A total of 90 patients were enrolled. Overall response rate, median PFS and median survival time in the docetaxel-plus-carboplatin group and the paclitaxel-plus-carboplatin group were 23% vs. 33%, 4.8 months vs. 5.1 months, and 17.6 months vs. 15.6 months, respectively. The docetaxel-plus-carboplatin group had a higher incidence of grade 3 or 4 neutropenia (88% vs. 60%). Conclusion: Both regimens were similarly effective in Japanese patients with advanced NSCLC.*

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Lung cancer is one of the most common malignancies and is the leading cause of cancer-related death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 85% of all cases of lung cancer. Platinum-based chemotherapy has been considered a standard treatment for advanced NSCLC. In addition, molecular-targeted therapy, including vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab, epidermal growth factor receptor (EGFR) inhibitors such as gefitinib or erlotinib, and anaplastic lymphoma kinase (ALK) inhibitors, has recently become a treatment option for specific subsets of patients, especially those with non-squamous cell lung cancer (2-5). These molecular targeted therapies have led to a paradigm shift of

treatment. Unfortunately, all patients with *EGFR*-mutant or ALK-positive lung cancer who receive EGFR or ALK inhibitors eventually experience disease relapse and require chemotherapy at some point during the course of treatment (4). Chemotherapy thus continues to play an important role in the management of NSCLC.

Docetaxel has been demonstrated to be effective against previously-untreated advanced NSCLC. Results of a large phase III trial found that docetaxel plus cisplatin was significantly superior to vindesine plus cisplatin in terms of overall response rate and overall survival (6). Carboplatin has shown broad equivalence to cisplatin in combination with chemotherapy for advanced NSCLC. To our knowledge, however, no clinical trial has directly compared docetaxel + carboplatin (DCarb) with paclitaxel plus carboplatin (PCarb) in patients with advanced NSCLC.

Fossella *et al*. reported a phase III study comparing docetaxel plus a platinum agent with vinorelbine plus cisplatin, performed by the TAX 326 Study Group (7). Docetaxel with cisplatin led to a better overall response and higher survival rate than docetaxel plus carboplatin, with a median survival time (MST) of 11.3 months, as compared with 9.4 months, respectively. However, that study was not designed to directly compare docetaxel plus cisplatin with docetaxel plus carboplatin. The therapeutic value of docetaxel with carboplatin as a front-line regimen for advanced NSCLC, thus remains unclear.

Millward *et al*. conducted a phase II study of docetaxel plus carboplatin in white and Asian patients with advanced NSCLC (8). The MST was 12.9 months, and multivariate analysis showed that ethnicity was a significant independent predictor of response and survival. Two clinical trials have evaluated docetaxel with carboplatin in Japanese patients with advanced NSCLC (9, 10). These trials reported a good MST of 12 months and 12.9 months, respectively. However, randomized phase II studies comparing docetaxel plus carboplatin with a standard regimen have yet to be performed on Asian patients with NSCLC. We therefore designed a randomized phase II study to compare the newer combination of DCarb with PCarb as standard treatment in patients with advanced NSCLC.

Patients and Methods

All patients enrolled in this study had cytologically- or histologically-confirmed diagnoses of NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or NSCLC not otherwise specified) with advanced stage IIIB or stage IV disease or relapse after surgical resection of NSCLC (regarded as stage IV). Other eligibility criteria were as follows: chemotherapy-naïve status; an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; a neutrophil count of at least 2.0×10^9 cells/l; a platelet count higher than 100.0×10^9 cells/l; a hemoglobin concentration of at least 90 g/l; serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentrations of less than two-times the upper limit of normal (ULN); serum total bilirubin and creatinine concentrations of less than the ULN; a creatinine clearance of 50 ml/min or higher (as calculated by the Cockcroft-Gault equation) (11); and an alveolar partial pressure of oxygen (PaO_2) of 70 Torr or higher or an oxygen saturation on pulse oximetry (SpO_2) of 94% or higher (while breathing room air). Patients were excluded if they had any of the following conditions: severe infection, pregnancy or breastfeeding; a previous malignancy within the previous five years (except for patients with cured carcinoma *in situ*); another active cancer; an allergy to polysorbate 80 or polyoxyethylene castor oil; evidence of interstitial lung disease on a plain chest x-ray film; uncontrolled co-morbidities such as malignant hypertension, congestive heart failure, myocardial infarction within the previous six months, arrhythmia requiring treatment, bleeding tendency, or diabetes mellitus; pleural or pericardial effusion requiring drainage; symptomatic brain metastasis; or peripheral neuropathy of more than grade 1.

All patients provided written informed consent. The study protocol was approved by the Institutional Review Boards of all participating institutions and by the Japan Multinational Trial Organization (JMTO) ethical committee. This study was conducted in accordance with the Declaration of Helsinki and was registered with UMIN 000001225 on June 30, 2008.

Study design and treatment. This was a randomized, phase II, open-label study. The primary end-point was the determination of progression-free survival (PFS). The secondary end-points were tumor response, survival (1-year survival rate, overall survival), and toxic effects. Patients were randomly assigned at a ratio of 2 to 1 to receive either DCarbo or PCarbo. Central randomization to each arm was performed with the use of Pocock and Simon's method (12). Stratification factors were PS (0 or 1), more than 5% weight loss within the previous six months (yes or no), and serum lactic dehydrogenase (LDH) concentration (abnormally high or not).

Patients in the DCarbo group received intravenous docetaxel (60 mg/m^2) over the course of 60 to 90 min and carboplatin [area under the curve (AUC) 6 mg/ml min] over the course of three hours on day 1 every 21 days for six cycles. Pre-medication, such as anti-emetic agents or corticosteroids, was given as required. In the PCarbo group, patients received intravenous paclitaxel (200 mg/m^2) and carboplatin (AUC 6 mg/ml min, same as in the DCarbo group) on day 1 every 21 days for six cycles. Creatinine clearance was calculated using the Cockcroft-Gault equation. The serum creatinine level (mg/dl) used in this equation was modified by adding 0.2 mg/dl, because an enzyme assay is used in Japan, whereas Jaffe's non-enzyme assay was used to develop this equation. Patients in the PCarbo group were given pre-medication with dexamethasone, diphenhydramine, and ranitidine or cimetidine. The use of additional antiemetics was left at the physician's discretion. Use of granulocyte-colony stimulating factor (G-CSF) was permitted any time during the study (except for prophylactic use) in both groups. In the absence of progressive disease or intolerable toxicity, patients in both groups received six cycles of chemotherapy.

Treatment could be delayed for up to 14 days if the neutrophil count was less than 1.5×10^9 cells/l and the platelet count was less than 75×10^9 cells/l on day 1 of each course. In the event of prolonged or complicated grade 4 neutropenia or thrombocytopenia, the dose of docetaxel was reduced by 10 mg/m^2, that of paclitaxel by 25 mg/m^2, or that of carboplatin by AUC 1 mg/ml min for the subsequent cycle of chemotherapy. Dose reduction was allowed

twice. Treatment could be delayed for up to 14 days if AST or ALT (or both) was more than 2.5-times higher than the ULN, the serum creatinine concentration was more than 1.5-times higher than the institutional ULN, or nonhematological toxicity of grade 2 or higher developed (except for nausea, vomiting, fatigue, loss of appetite, mild electrolyte abnormalities, and alopecia) developed.

Patients were assessed every two cycles, and the objective response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 (13). The best response in individual patients was derived from investigator-reported data. Objective response rates were confirmed by at least one sequential tumor assessment. Toxic effects were graded in accordance with the National Cancer Institute Common Toxicity Criteria, version 2.0 (14). The numbers and frequencies of each adverse event were respectively summarized for any grade and for grade 3 or higher in each treatment group. The MST with 95% confidence intervals (CI) and the probability of 1-year survival with 95% CI were calculated by the Kaplan-Meier method for each group.

Statistical plan and analysis. The primary end-point was PFS. The main objective of the study was to estimate the PFS rate at six months in the DCarbo group. The median PFS in the DCarbo group was predicted to be about 150 days on the basis of the results of previous studies. The PFS rate at six months was thus assumed to be 45%. Given that the range of the 90% CI at six months is 0.1 or less, we estimated that at least 60 patients would be required in the DCarbo group. Because patients were randomly assigned to either the DCarbo group or PCarbo group at a ratio of 2:1, the target number of patients in the latter group (calibration group) was 30. Hazard ratios (HR) and 95% CIs were calculated with a Cox proportional-hazards model.

Results

Patients' characteristics. A total of 90 patients were enrolled between June 2007 and September 2008 at 15 institutions in Japan. All patients were eligible for analysis. Sixty patients were assigned to the DCarbo group and 30 were assigned to the PCarbo group (Figure 1). The patients' characteristics for both groups were shown in Table I. The baseline characteristics of patients in the DCarbo group were similar to those in the PCarbo group.

Tumor response and survival. The total number of administered cycles of chemotherapy was 230 in the DCarbo group and 139 in the PCarbo group. The median follow-up time was 15.8 months.

Sixty patients began chemotherapy in the DCarbo group, and 19 completed six cycles according to protocol. The mean number of administered cycles of chemotherapy was 4.0 (range, 1 to 6). Dose modification was carried out once in 17 patients (28%) and more than once in 23 patients (38%). Treatment was delayed in 11 patients (18%). The reasons for treatment discontinuation before the completion of six cycles of DCarbo were disease progression (n=18), dose modification necessitated by adverse events more than twice (n=12), and withdrawal of treatment by the patient (n=6) or investigator (n=5). In the PCarbo group, 30 patients began chemotherapy, and 14 completed six cycles. The mean number of administered cycles was 4.6 (range, 1 to 6). Dose modification was carried out once in seven patients (23%) and more than once in seven patients (23%). Treatment was delayed in 10 patients (33%). The reasons for discontinuation of PCarbo before the completion of six cycles were disease progression (n=6), withdrawal of treatment by the patient (n=5), dose modification necessitated by adverse events more than twice (n=4), and withdrawal of treatment by the investigator (n=1).

The overall response rate (based on the best confirmed response during study treatment) was 23% [14 out of 60 patients with partial response (PR); 95% CI=13%-36%] in the DCarbo group and 33% (10 out of 30 patients with PR; 95% CI=17%-53%) in the PCarbo group (Table II). No patient had a complete response. Stable disease was obtained in 31 patients (52%; 95% CI=38%-65%) in the DCarbo group and 15 patients (50%; 95% CI=31%-69%) in the PCarbo group. The Median PFS was 4.8 months (95% CI=3.9-7.2 months) in the DCarbo group and 5.1 months (95% CI=4.4-6.4 months) in the PCarbo group. The PFS rate at six months was 42% (90% CI=31%-52%) in the DCarbo group and 40% (90% CI=25%-54%) in the PCarbo group (Figure 2). The hazard ratio of DCarbo referenced to PCarbo was 0.86 (95% CI=0.55-1.36). The MST was 17.6 months (95% CI=10.2-22.9 months) in the DCarbo group and 15.6 months (95% CI=9.3-20.8 monts) in the PCarbo group (Figure 3). The 1-year survival rate was 60% in both groups (90% CI=49%-70% in the DCarbo group and 44%-73% in the PCarbo group). The hazard ratio of DCarbo compared to PCarbo was 0.77 (95%CI=0.47-1.26).

Toxicity. All patients were assessable for toxicity (Table III). Patients in the DCarbo group had a higher incidence of grade 3 or 4 neutropenia than those in the PCarbo group (88% *vs*. 60%, 95% CI=77%-95% *vs*. 41%-77%). The PCarbo group had a higher incidence of grade 2 or more sensory neuropathy (37% *vs*. 3%, 95% CI=20%-56% *vs*. 0%-12%), myalgia (13% *vs*. 0%, 95% CI=4%-31% *vs*. 0%-6%), and arthralgia (20% *vs*. 2%, 95% CI=8%-39% *vs*. 0%-9%) than the DCarbo group. There were no major differences between the two groups regarding any other toxic effects (Table III).

One treatment-related death was reported in the DCarbo group. Acute respiratory distress syndrome (ARDS) developed in a 76-year-old woman two months after the end of the fifth, final cycle of treatment. Five days after the onset of respiratory failure, the patient had an acute myocardial infarction and died two days later. The patient's attending physician judged that the relation to treatment was "not definite." An independent data monitoring committee judged

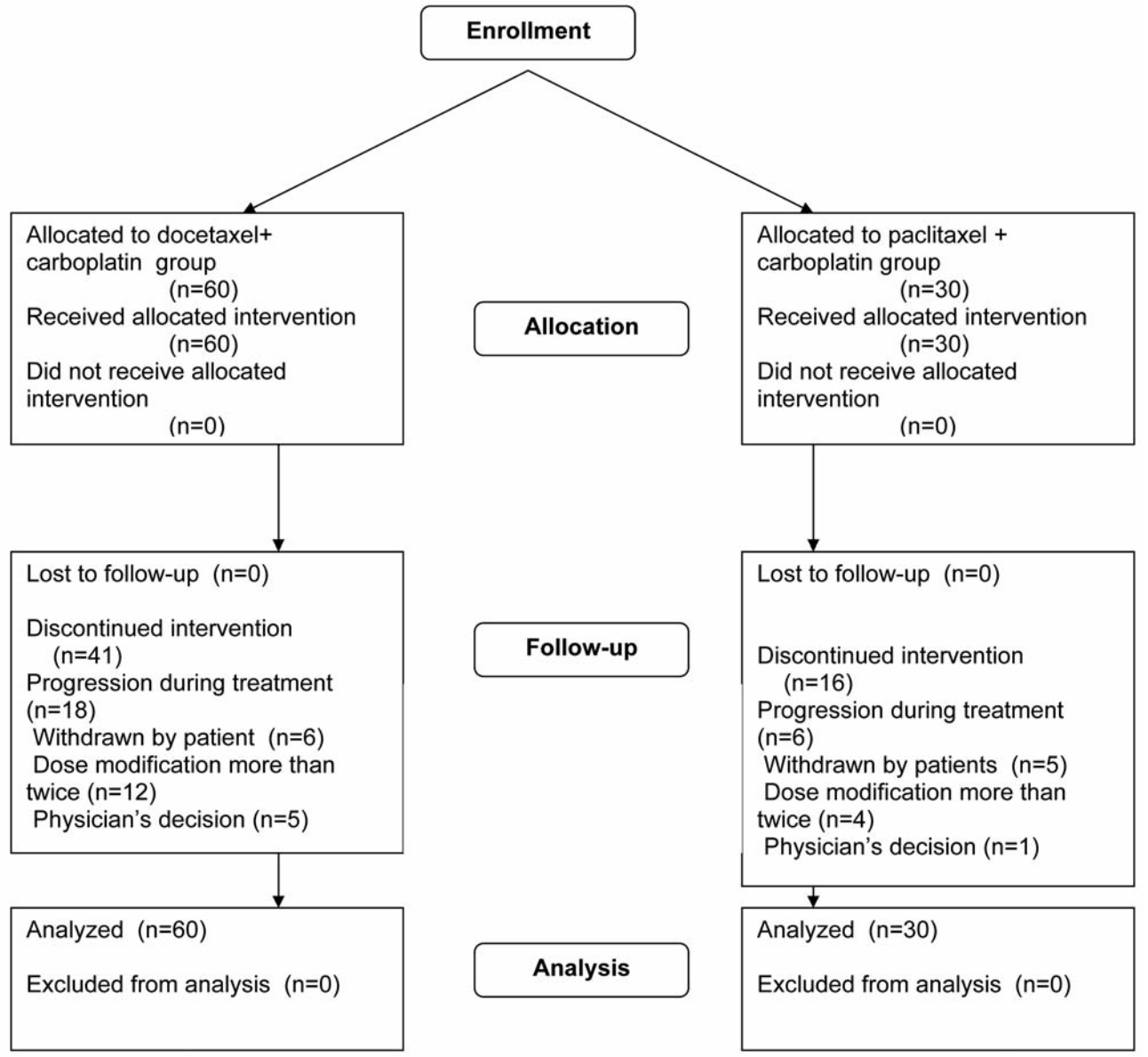

Figure 1. *Study design and patient flow. n: Number of patients.*

that the relation of death to the study treatment was not definite, but possible.

Discussion

This randomized phase II trial comparing DCarbo with PCarbo is the first of this kind to be performed in Asia. Our results suggest that both regimens are similar in terms of PFS and overall survival. The PFS of 4.8 (95% CI=3.9-7.2) months and MST of 17.6 (95% CI=10.2-22.9) months in the DCarbo group were favorable.

Asian ethnicity may contribute to some degree to better results in patients who receive DCarbo, as reported by Millward *et al*. (8). Three large phase III trials performed on Japanese patients with advanced NSCLC have included paclitaxel + carboplatin as one treatment arm (15-17). In these studies, the number of patients who received PCarbo was 281 (Okamoto *et al*.) (15), 197 (JMTO LC 00-03 study) (16), and 145 (Four-Arm Cooperative Study) (17), respectively. The dose of carboplatin was AUC 6 mg/ml min, with paclitaxel given at a dose of 200 mg/m^2 in two studies (15, 17) and 225 mg/m^2 in the other (16). The median PFS

Table I. *Patients' characteristics.*

	Docetaxel + carboplatin c (%) (n=60)	Paclitaxel + arboplatin (%) (n=30)
Age (median) (years)	67.5	65.5
Male/female	43/13 (78/22)	22/8 (73/27)
Body weight loss>5% Yes /no	11/49 (18/82)	5/25 (17/83)
Performance status 0/1	19/41 (32/68)	7/23 (23/77)
Histology Sq/Ad/La/Other	13/36/2/9 (22/60/3/15)	10/17/0/3 (33/57/0/10)
Stage IIIB/IV	24/36 (40/60)	10/20 (33/67)
Naïve/relapsed	53/7 (88/12)	26/4 (87/13)
LDH Normal/abnormally high	44/16 (73/27)	21/9 (70/30)
Prior radiotherapy	3 (5)	3 (10)

Sq: Squamous cell carcinoma, Ad: adenocarcinoma, La: large cell carcinoma, LDH: lactate dehydrogenase.

Table II. *Overall response and survival data.*

Regimen	Docetaxel + carboplatin	Paclitaxel + carboplatin
Number of patients	60	30
Response rate (95%CI)	23% (13-36%)	33% (17-53%)
Median PFS (95% CI), months	4.8 (3.9-7.2)	5.1 (4.4-6.4)
PFS rate (90% CI)*	42% (31-52)	40% (25-54)
HR (95% CI)	0.86 (0.55-1.36)	Referent
Median OS (95% CI), months	17.6 (10.2-23.0)	15.5 (9.4-20.8)
HR (95% CI)	0.77 (0.47-1.26)	Referent
1-Year survival rate (90% CI)	60% (49-70)	60% (44-73)

MST: Median survival time, CI: confidence interval, HR: hazard ratio, PFS: progression-free survival , OS: overall survival. *At six months.

Table III. *Toxicities experienced during study period.*

Toxicity	Docetaxel+ carboplatin % (95% CI) N=60	Paclitaxel+ carboplatin % (95% CI) N=30
Grade 3 or more Neutropenia	88 (77-95)	60 (41-77)
Grade 3 or more Anemia (hemoglobin)	12 (5-23)	7 (1-22)
Grade 3 or more Thrombocytopenia	0	3 (0-17)
Grade 3 or more Frbrile neutropenia	17 (8-29)	13 (4-31)
Grade 2 or more Nausea	28 (18-41)	17 (6-35)
Grade 2 or more Vomiting	12 (5-23)	10 (2-27)
Grade 2 or more Sensory neuropathy	3 (0-12)	37 (20-56)
Grade 2 or more Myalgia	0	13 (4-31)
Grade 2 or more Arthralgia	2 (0-9)	20 (8-39)
Possible TRD (ARDS)	1	0

CI: Confidence interval, TRD: treatment-related death, ARDS: acute respiratory distress syndrome.

or time to progression was 4.8, 5.8, and 4.5 months, and the MST was 13.3, 14.1, and 12.3 months, respectively. These results are similar to those of the present trial, obtaining a PFS of 5.1 months and an MST of 15.6 months, and suggest that Japanese patients have a good response to taxane-based chemotherapy. C1236T polymorphism in the ATP-binding cassette sub-family B member-1 (*ABCB1*) gene is significantly related to docetaxel clearance (18). Gandara *et al*. reported ethnic differences in the metabolism of taxanes between American and Japanese patients with lung cancer in a common-arm analysis of PCarbo, performed jointly in the United States and Japan (19).

Differences in the allelic distribution of genes involved in paclitaxel disposition or DNA repair [cytochrome *P450* 3A4 (CYP3A4)*1B and excision repair cross-complementation group 2 (*ERCC2*) K751Q] were observed between Japanese and American patients. Resulting metabolic differences in taxane metabolism may consequently contribute to better outcomes in Asian patients with lung cancer who receive taxanes.

In our study the dose of docetaxel was 60 mg/m^2 and that of carboplatin was AUC 6 mg/ml min. This dose of docetaxel is generally used in Japan to treat NSCLC. When combined with cisplatin, the dose of docetaxel used in Japan may be slightly lower the one that used in other countries (6). However, the results of Japanese studies in terms of PFS or overall survival are not inferior to those of studies performed in other countries, where docetaxel is usually given at a dose of 75 mg/m^2 (7). On the other hand, most Japanese studies have used cisplatin at a dose of 80 mg/m^2, which is slightly higher than that used in other countries (75 mg/m^2). The modest differences in the doses of chemotherapeutic agents may not have had a major influence on PFS or overall survival. Brunetto *et al*. reported that the dose intensity of platinum-doublet regimens including cisplatin or carboplatin with either vinorelbine or gemcitabine did not have an impact on survival or time-to-progression in patients with NSCLC (20).

A phase III study comparing DCarbo with PCarbo as first-line chemotherapy was performed in 1,077 patients with ovarian cancer (21). Docetaxel (75 mg/m^2) or paclitaxel (175 mg/m2) with carboplatin to (AUC 5 mg/ml min) was administered every three weeks for six cycles.

The study also concluded that DCarbo is similar to PCarbo in terms of PFS and response, but recommended that longer follow-up is required before making a definitive statement on survival. DCarbo was considered an alternative first-line regimen for chemotherapy in patients with ovarian cancer. As for toxicity, DCarbo was associated with

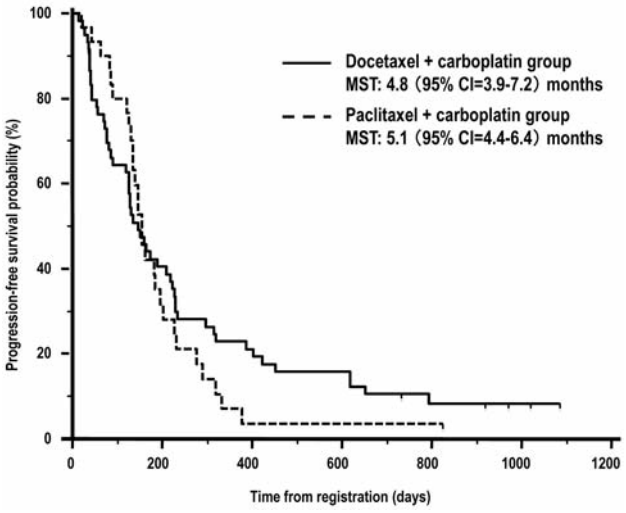

Figure 2. *Progression-free survival. MST: Median survival time, CI: confidence interval.*

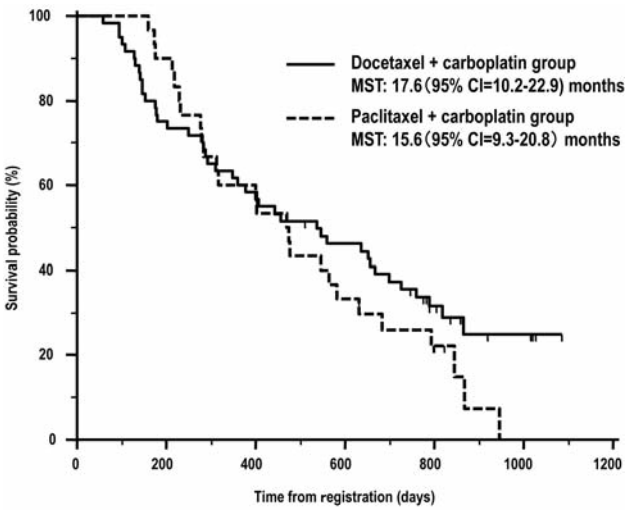

Figure 3. *Overall survival. MST: Median survival time, CI: confidence interval.*

substantially less overall and grade 2 or more neurotoxicity than PCarbo. On the other hand, DCarbo led to a higher incidence of grade 3 or 4 neutropenia than did PCarbo. Similar trends were noted in our study: DCarbo had a lower incidence of grade 2 or more sensory neuropathy (3% *vs.* 37%), but a higher incidence of grade 3 or more neutropenia (87% *vs.* 60%) as compared with PCarbo. Although myelosuppression was also frequently associated with DCarbo in our study, this adverse effect was not dose-limiting.

Recently, the survival of patients with NSCLC has improved, in part because of improved treatments or perhaps because of selection bias. The longer the survival, the more problematic is chronic toxicity such as neurotoxicity. Such toxicity negatively affects the quality of life of patients with NSCLC. This is especially true for those tested with PCarbo regimens (22). Even if the dose of paclitaxel is reduced from 225 mg/m^2 to 200 mg/m^2, the problem of neurotoxicity persists. DCarbo would, thus, be the preferred regimen to avoid severe neurotoxicity.

The treatment-related death in the DCarbo group in our study was reviewed by a safety committee. ARDS occurred as late as two months after the end of the patient's fifth, final cycle of treatment. The relation of death to chemotherapy with DCarbo was considered not definite, but possible.

Our study had several important limitations. We studied only Japanese patients, and it remains unclear whether our results can be extrapolated to other ethnic groups. Our study group comprised of patients with all histological types of NSCLC, and information on mutations in the *EGFR* gene was not obtained. In addition, the doses of docetaxel and carboplatin differed from those used in Western studies of patients with NSCLC.

Conclusion

Docetaxel plus carboplatin is considered an alternative first-line chemotherapeutic regimen for patients with newly-diagnosed advanced NSCLC, at least in Asia. In the future, this regimen might be combined with other treatments, such as molecular targeted therapy.

Conflicts of Interest

None.

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