Supporting Information

Figure S1 Comparison of cell recovery rate using the microcavity array (MCA) system and an isolation by size of epithelial tumor cell (ISET) filter. Non-small cell lung cancer cell line NCI-H358 was spiked into whole blood at a volume of 100 cells/mL to perform 3 separate tests of circulating cancer cell recovery using an MCA (pore size = 8 μm) and a track-etched polycarbonate ISET filter (pore size = 8 μm; Nucleopore).
(TIFF)

Figure S2 Bland–Altman plots of agreement between circulating tumor cell (CTC) test results obtained for non-small cell lung cancer (NSCLC; a) and small cell lung cancer (SCLC; b) patients using the CellSearch and microcavity array (MCA) systems. The solid horizontal line represents the mean difference and the dashed lines the limits of agreement (mean difference +/−2SD). In NSCLC, the mean difference was 50.1 (95%CI, 11.1 to 89.1), limits of agreement (-125.8 to 226.0) with the difference between systems becoming disproportionately greater with higher average CTC-count. In SCLC, the mean difference was 202.6 (95%CI, −116.7 to 521.9), limits of agreement (-1162.0 to 1567.2) with no bias observed between systems except for subjects with extremely high titer of CTCs.
(TIFF)

Table S1 Evaluation of sensitivity of microcavity array (MCA) system for circulating tumor cell (CTC) detection. Sensitivity testing was performed using artificial samples created by adding 1 and 3 cultured NCI-H358 cells to healthy donor blood samples. Individual cells were selected by micropipette under direct visualization, spiked into 7.5 mL aliquots of blood, and the resulting blood samples processed using the MCA system in 3 separate tests.
(DOC)

Author Contributions

Conceived and designed the experiments: MH H. Kenmotsu YK T. Yoshino TN TM NY. Performed the experiments: MH T. Yoshikawa RW SO. Analyzed the data: MH H. Kenmotsu YK T. Yoshikawa TN RW SO KM NY. Contributed reagents/materials/analysis tools: H. Kenmotsu TN T. Takahashi HM YN AT TS AO HA H. Kanbara KY NY. Wrote the paper: MH H. Kenmotsu YK T. Yoshino T. Yoshikawa TN T. Tanaka TM NY.

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Case report

An extremely rare case of small-cell lung cancer harboring variant 2 of the *EML4-ALK* fusion gene

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ABSTRACT

Anaplastic lymphoma kinase (*ALK*) fuses *echinoderm microtubule-associated protein-like 4* (*EML4*) to acquire a transforming activity in lung adenocarcinomas. However, the presence of an *EML4-ALK* fusion gene in other lung cancer histologies is an extremely rare phenomenon. A 43-year-old female was referred to our department due to dyspnea on effort and left back pain. Computed tomography (CT) showed a large mass in the upper lobe of the left lung and a massive left pleural effusion, while a CT-guided needle biopsy confirmed a diagnosis of small-cell lung cancer (SCLC). Surprisingly, the tumor was genetically considered to harbor the *EML4-ALK* fusion gene (variant 2). Although the patient underwent two regimens of cytotoxic chemotherapy for SCLC, she died approximately seven months after the administration of first-line chemotherapy. Our analysis of 30 consecutive patients with SCLC for *EML4-ALK* revealed that two patients, including the current patient and a patient we previously reported, harbored the *EML4-ALK* fusion gene.

1. Introduction

Oncogenic driver mutations, such as *epidermal growth factor receptor* (*EGFR*), *anaplastic lymphoma kinase* (*ALK*) and so on, have been shown to play essential roles in tumorigenesis, survival and proliferation in lung cancer, especially adenocarcinoma [1,2]. Driver mutations have attracted attention as potential targets of kinase inhibitors [2,3]. In addition to the molecular pathogenesis of lung adenocarcinomas, genetic insights into the pathogenesis of squamous cell carcinoma and small-cell lung cancer (SCLC) have recently been reported [4,5]. However, to the best of our knowledge, there is only one case of *echinoderm microtubule-associated protein-like 4* (*EML4*)-*ALK*-positive SCLC combined with adenocarcinoma, which we previously reported [6]. We herein report a genetically rare case of SCLC harboring an *EML4-ALK* fusion gene and describe the patient's clinical course.

2. Case report

A 43-year-old female ex-smoker of five pack-years was referred to our hospital due to dyspnea on effort and left back pain. A chest X-ray showed a large mass shadow in the left upper lung field and decreased transparency in the left lower lung field. Computed tomography (CT) revealed a large, irregular mass with a maximum diameter of 10 cm in the left upper lobe invading the 4th rib (Fig. 1A) and a massive left pleural effusion. Laboratory examinations revealed elevations in the levels of neuron specific enolase (NSE; 37.7 ng/ml) and pro-gastrin-releasing peptide (ProGRP; 1740 ng/ml), whereas no abnormalities were observed in other tumor markers. A CT-guided tumor biopsy was then performed, and the tumor was pathologically diagnosed as small-cell lung cancer (SCLC) with immunoreactivity to synaptophysin and CD56 (Fig. 2A and B), while no immunoreactivity against thyroid transcription factor-1 (TTF-1) was observed (Fig. 2C). The clinical stage was ultimately determined to be IV (cT3N0M1a: extensive disease). Multiplex reverse transcription-polymerase chain reaction (RT-PCR) and direct sequencing methods revealed the tumor to harbor variant 2 of the *EML4ALK* fusion gene (Fig. 2D), whereas no mutations of *epidermal growth factor receptor* (*EGFR*) or *TP53* were observed (data not shown). As the performance status of the patient

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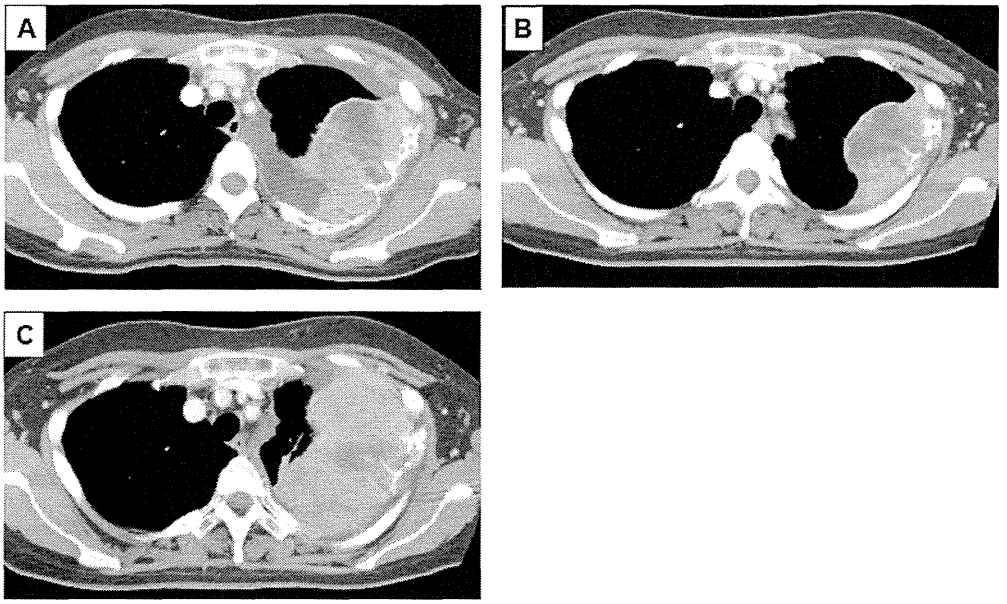

Fig. 1. Computed tomography showed a large mass invading the left 4th rib. (A) CT showed the mass approximately 2.5 (B) and four months (C) after the administration of first-line chemotherapy.

was 3, carboplatin (CBDCA) in combination with etoposide (VP-16) was administered as a first-line regimen with daily thoracocentesis of the pleural effusion. Since the PS improved from 3 to 0 following the administration of one cycle of CBDCA + VP-16, the patient underwent three cycles of cisplatin (CDDP) + VP-16. Although a partial response (PR) was achieved (Fig. 1B) and the levels of NSE and ProGRP decreased (9.9 and 409 ng/ml, respectively) after four cycles of chemotherapy, progressive disease was observed 1.5 months

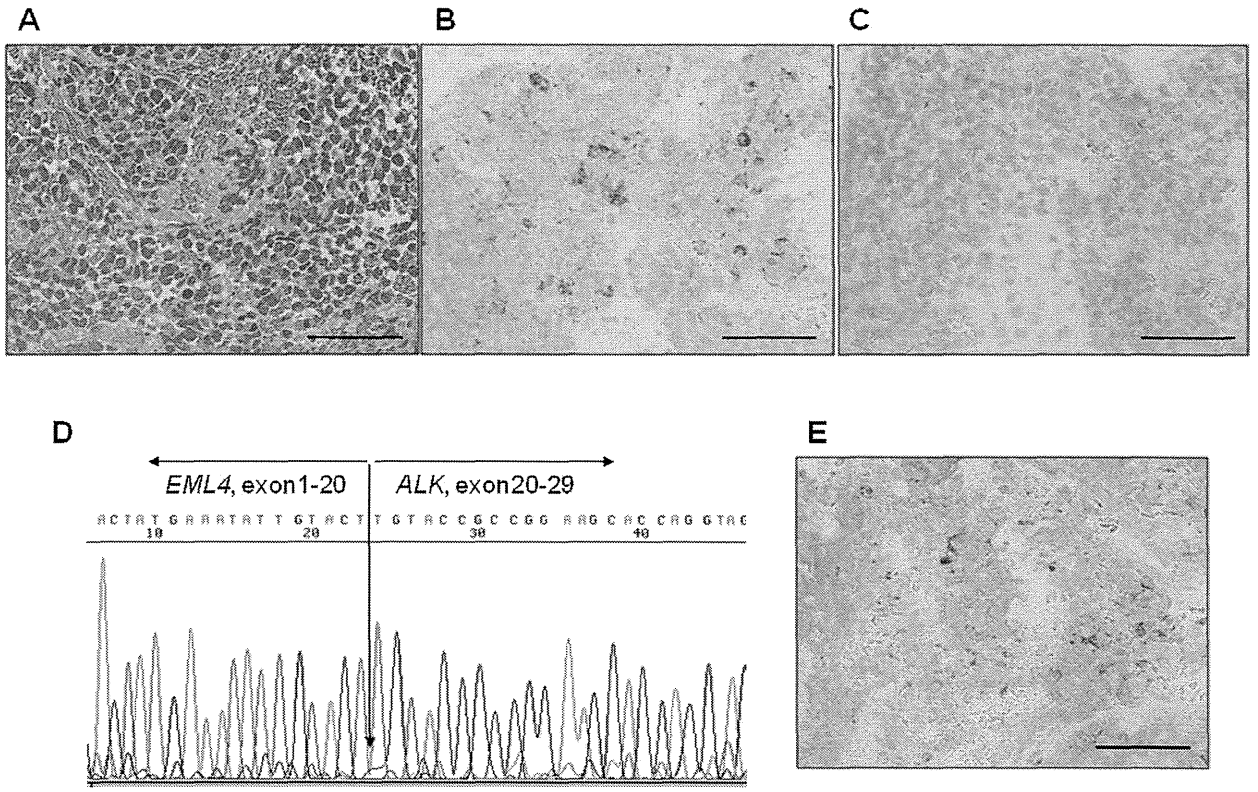

Fig. 2. (A) Microscopic findings of the tumor indicated small, round cells with abundant chromatin. (B) Immunohistochemistry using a specific antibody against synaptophysin (27G12, Novocastra) showed the tumor to be positively stained. (C) Immunohistochemistry using an antibody with specificity for thyroid transcription factor-1 (TTF-1; 8G7G3/1, Dako) showed that the tumor did not have immunoreactivity for TTF-1. (D) The direct sequencing method identified variant 2 of the *echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase* (*ALK*) fusion gene. (E) Immunostaining using an antibody that specifically detects ALK (5A4, Nichirei) revealed immunopositivity of the tumor for ALK. Scale bar (A–C, E): 50 μm.

after the confirmation of a PR (Fig. 1C). Thereafter, a CT-guided biopsy was performed again, and the SCLC histology was reconfirmed. Furthermore, the presence of the *EML4-ALK* fusion gene was confirmed on immunohistochemistry (IHC) using an antibody that specifically detects ALK (Fig. 2E). Although amrubicin was then administered, the disease continued to progress. Approximately six months after the administration of the first-line chemotherapy, the patient was transferred to another hospital for hospice care and died 18 days after the transfer. Based on her clinical course, the progression-free survival (PFS) and overall survival (OS) from the administration of the first-line therapy were approximately four and seven months, respectively.

3. Discussion

Gene mutations in tyrosine kinases play essential roles in the pathogenesis of lung adenocarcinoma and have attracted much attention as potential therapeutic targets in the treatment of adenocarcinoma. The *ALK* gene has been shown to fuse the *EML4* gene, and as a consequence, to possess a transforming activity [1]. Importantly, tumors with the *EML4-ALK* fusion gene, the second most well-known tyrosine kinase in lung adenocarcinoma, can be successfully treated with ALK inhibitors [7]. Mutations of the *EGFR* gene in SCLC have already been identified (5/122: 4%) [8], and integrative genomic analyses have revealed mutations of tumor suppressor genes (TP53 and RB1), histone modifiers (MLL1) and so on in SCLC. However, to the best of our knowledge, there has been only one case of an SCLC patient harboring the *EML4-ALK* fusion gene [6]. In our previous case, fusion of the *ALK* gene to the *EML4* gene was intriguingly detected only in the SCLC component of the resected combined adenocarcinoma with SCLC. Although this previous patient harbored variant 1 of the *EML4-ALK* fusion gene, variant 2 of the fusion gene was identified in the current case. Based on these findings, there are considered to be multiple *EML4-ALK* variants in SCLC patients as well as adenocarcinoma patients. We analyzed 30 consecutive SCLC patients whose RNAs were available for RT-PCR and direct sequencing methods between April 2010 and March 2012. Two of the patients, the present patient and the patient we previously reported [6], were found to harbor the fusion gene. Although a positive reaction of IHC for the ALK protein expression without *ALK* fusion was reported to be found in a patient with SCLC [9], this does not apply to the current case because the fusion was detected using RT-PCR and direct sequencing methods. Furthermore, the possibility of the transformation of adenocarcinoma into SCLC, which is associated with the acquisition of resistance to EGFR-tyrosine kinase inhibitors (TKIs), should be taken into consideration [10]. However, this mechanism does not apply to the present patient, since no EGFR-TKIs were administered because of the absence of the *EGFR* mutations.

One of the limitations of the current case report is that the tumor was diagnosed to be SCLC by a biopsy sample. Although biopsy samples do not always reflect the exact histology of the whole tumor, and the absence of lymphadenopathy and *p53* mutations, which occur in more than 90% of all SCLCs [11], is relatively rare, the SCLC histology was confirmed by several findings in the present case. First, a CT-guided biopsy before and after the first-line chemotherapy diagnosed the tumor to be morphologically SCLC. Second, immunoreactivity of the tumor for synaptophysin and CD56 was observed. Third, the levels of tumor markers associated with SCLC, i.e., NSE and ProGRP, were elevated, while no elevation was observed in the levels of carcinoembryonic antigen and cytokeratin 19 fragment. Finally, combination chemotherapy with platinum plus VP-16, one of the standard regimens for patients with SCLC, led to a partial response. With regard to TTF-1 expression, TTF-1 was reported to be expressed in all adenocarcinomas harboring the *ALK* rearrangement [12], and TTF-1 expression was also observed in about 80% of SCLCs [13]; however, the current patient showed no expression of TTF-1, as shown in Fig. 2C, which was different from the results we previously reported in Ref. [6], and no definite correlation between TTF-1 expression and the *EML4-ALK* rearrangement in SCLC has been demonstrated so far. Although these findings show an apparently rare presentation of SCLC in the current patient, future studies would help to elucidate the characteristics of patients with SCLC harboring the *EML4-ALK* rearrangement.

Although SCLC manifests with aggressive features, such as rapid progression, these tumors are generally sensitive to chemotherapy. For first-line therapy, the response rate, median PFS and OS range from 67.5 to 84.4%, 4.7–6.9 months and 9.4–12.8 months, respectively [14,15]. Although the current patient achieved a PR after undergoing four cycles of platinum-based chemotherapy, the PFS and OS were much worse than those of historical controls. As a reason for the poor clinical course of the present patient, there is a possibility that the fusion gene affects sensitivity to chemotherapy. There have been two reports on chemosensitivity in patients with the *EML4-ALK* fusion gene [16,17]. Lee et al. reported that *ALK*-positive non-SCLC patients would benefit significantly from pemetrexed chemotherapy, whereas Takeda et al. demonstrated that the efficacy of first-line platinum-based chemotherapy does not depend on the presence or absence of the *EML4-ALK* fusion gene. Therefore, although the significance of *ALK*-positivity for chemosensitivity has yet to be clarified, *EML4-ALK* fusion may be involved in the sensitivity of platinum-based chemotherapy.

4. Conclusion

We herein reported a very rare case of SCLC in which the patient harbored variant 2 of the *EML4-ALK* fusion gene. Although the frequency and significance of the fusion gene in SCLC patients has not been determined, this phenomenon suggests that SCLC patients harboring the *EML4-ALK* fusion gene can be successfully treated with ALK inhibitors.

Conflict of interest statement

Drs. Takenoyama, Shiraishi, Hirai, Yamaguchi, Seto and Ichionose have conflicts of interest with Pfizer, AstraZeneca and Chugai to disclose as shown in the attached file. The other authors have no conflicts of interest to declare.

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CASE REPORT

Cystic brain metastasis of non-small-cell lung cancer successfully controlled with Ommaya reservoir placement

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Abstract A 68-year-old male presented with hoarseness and anarthria. Computed tomography showed an irregular nodular shadow in the upper lobe of the left lung with swollen multiple lymph nodes. Magnetic resonance imaging revealed a large cystic mass in the left hemisphere of the brain and multiple brain metastases in the bilateral hemispheres. A direct biopsy with bronchoscopy of the pulmonary nodule revealed the tumor to be an adenocarcinoma clinically diagnosed as stage IV. Since the largest brain metastasis continued to grow despite the administration of whole brain irradiation, insertion of an Ommaya reservoir in the cystic lesion was performed. This resulted in a reduction of the size of the brain tumor, and the patient's neurological symptoms improved. After the Ommaya reservoir was placed, stereotactic radiosurgery was performed on the largest lesion. The patient is doing well at 6 months after the Ommaya reservoir was inserted and is currently undergoing chemotherapy. In conclusion, the placement of an Ommaya reservoir may therefore be a potentially useful therapeutic procedure to improve the neurological symptoms and performance status in non-small-cell lung cancer patients with cystic brain metastasis, thereby allowing further neurosurgical therapy and chemotherapy.

Keywords Non-small-cell lung cancer · Cystic brain metastasis · Ommaya reservoir

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Introduction

An Ommaya reservoir is a device placed under the skin of the head with the tip of the catheter positioned into the ventricles or within cystic lesions in the brain [1]. This device helps to drain the cerebrospinal fluid and contents of cystic lesions. Additionally, intraventricular administration of some drugs, such as amphotericin B, primethamine and methotrexate, can be conducted through this device [1, 2]. Although the usefulness of this device for treating cystic lesions in the brain has been previously reported, few reports of cystic brain metastases from lung cancer being controlled by the insertion of an Ommaya reservoir have been published in the English literature [3, 4]. In this report, we present a case of non-small-cell lung cancer (NSCLC) with a large cystic brain metastasis that was successfully controlled with the insertion of an Ommaya reservoir.

Case report

A 68-year-old male ex-smoker was referred to our hospital due to hoarseness and anarthria. Computed tomography (CT) revealed an irregular nodular shadow in the left upper lobe of the lung with enlargement of the left hilar, para-aortic and left subclavicular lymph nodes, which showed abnormal uptake of F-18 fluorodeoxyglucose on positron emission tomography/computed tomography (Fig. 1a). Magnetic resonance imaging (MRI) revealed a large mass in the left hemisphere (Fig. 1b, c) and multiple small nodules in the bilateral hemispheres (Fig. 1b, arrow). T1-weighted images showed very low signal intensity and T2-weighted images showed very high signal intensity in the largest mass consistent with the findings of a cystic lesion.

Bronchoscopy was then performed and a direct biopsy revealed the tumor to be an adenocarcinoma. Based on these findings, the clinical stage was considered to be stage IV (cT1bN3M1b).

Due to the presence of multiple brain metastases with the one larger than 3 cm, 30 Gray (Gy) of whole brain irradiation (WBI) was administered. Despite the administration of WBI, the largest cystic tumor continued to grow, and the surrounding edema expanded and the midline shifted (Fig. 1d). This resulted in worsened anarthria and the emergence of Gerstmann's syndrome. Various neurosurgical procedures were considered, and insertion of an Ommaya reservoir was chosen to minimize invasiveness. A dome-shaped plastic device was placed under the skin of the left head with a catheter positioned into the cavity of the cystic lesion without any complications (Fig. 2a). MRI and CT performed about 1 month after MRI as shown in Fig. 1c, revealed a reduction in the size of the tumor and the amount of surrounding edema (Fig. 2b, c). Crucially, the neurological symptoms improved. Since the cystic tumor was reduced from 4.7 to 2.9 cm, 20 Gy of stereotactic radiosurgery (SRS) was administered. Although the cystic tumor remained the same size after the SRS was completed, no punctures were needed to drain the fluid. The patient is doing well at 6 months after the insertion of the Ommaya reservoir and is currently undergoing chemotherapy with carboplatin and pemetrexed due to the improvement of performance status (PS) from 3 to 1.

Discussion

Ommaya reservoirs were originally developed to achieve aseptic access to ventricular cerebrospinal fluid. The device consists of an indwelling subcutaneous capsule made of silicone rubber that fits into a cranial burr-hole and is connected to a ventricular catheter. Percutaneous needle punctures can be repeatedly made through the dome of the capsule. This device is used for the administration of chemotherapy for neoplasia, cystic tumor drainage, ventricular drainage, special diagnostic studies and sampling of cerebrospinal fluid [1, 2]. In addition, diverse types of diseases, such as primary brain tumors, fungal meningitis, toxoplasmosis and head injury, can be indications for the placement of the device [1]. However, few reports of cystic brain metastasis from lung cancer being controlled with the

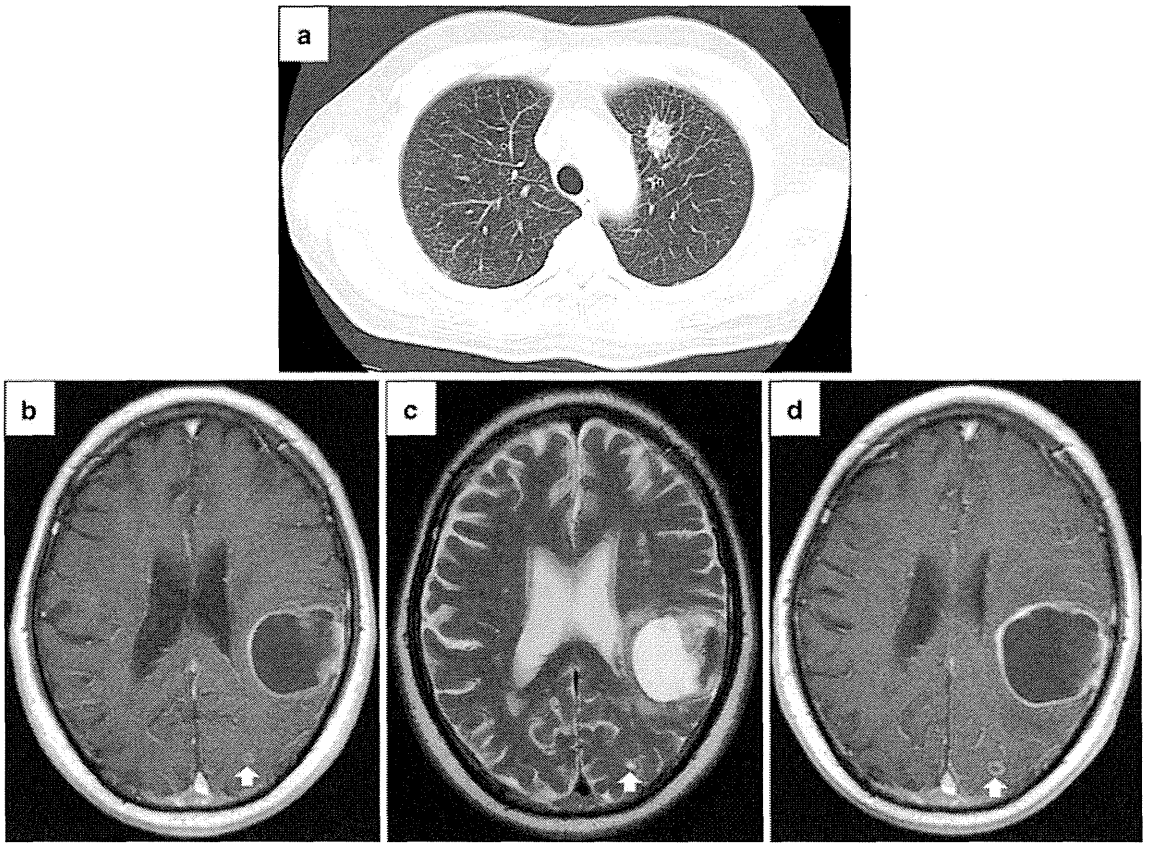

Fig. 1 CT and MRI findings. CT shows an irregular nodule in the left upper lobe of the lung (**a**). T1- and T2-weighted images indicate a large cystic brain tumor and multiple small cystic nodules (*arrow*) before the administration of WBI (**b**, **c**). T1-weighted images show the tumor after WBI (**d**)

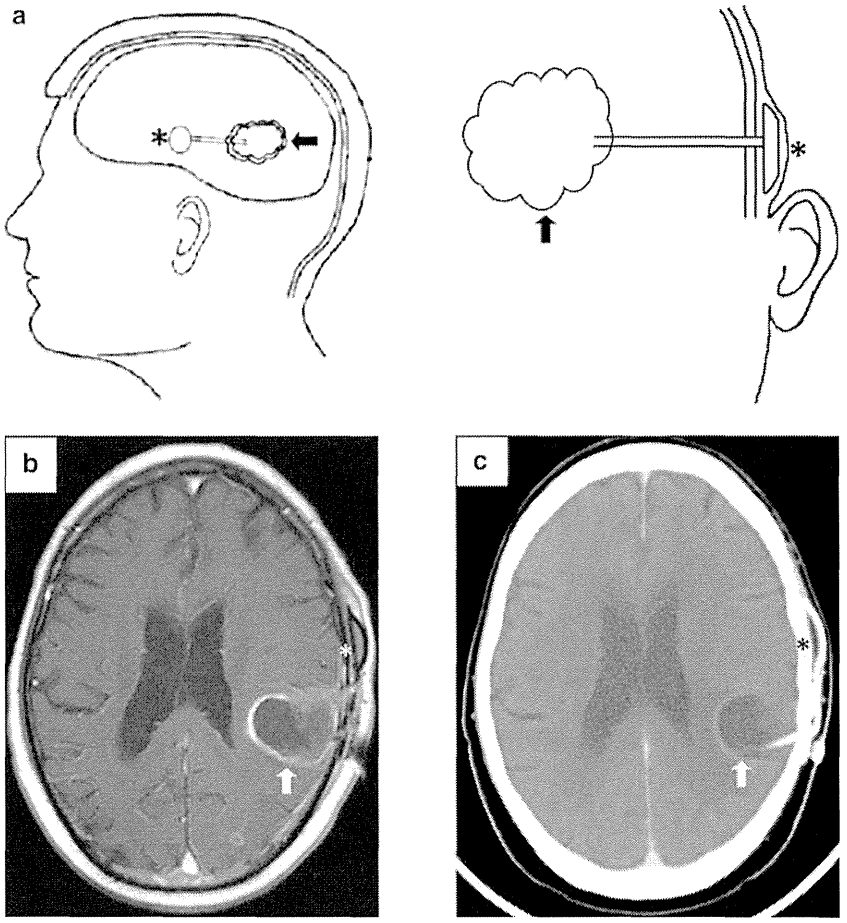

Fig. 2 Ommaya reservoir placement. Left lateral and frontal views of the head show the Ommaya reservoir (*asterisk*) placed under the skin of the left head with a catheter positioned into the cavity of the cystic lesion (*arrow*) (**a**). MRI and CT images show the inserted Ommaya reservoir (**b**, *asterisk*, **c**)

insertion of an Ommaya reservoir have been published in the English literature [3, 4]. Takeda and colleagues reported the case of a SCLC patient with solitary cystic brain metastasis who was successfully treated with a stereotactically inserted Ommaya reservoir followed by neurosurgical resection of the tumor, and the survival time of the patient after the insertion of the device was 4 months [3]. In addition, the usefulness of SRS following Ommaya reservoir placement has been reported in patients with large cystic metastatic brain tumors, including lung and breast cancer, with a median survival time of 7 months after the insertion of the device [4]. However, these papers did not mention chemotherapy after an Ommaya reservoir was placed. In the present case, a metastasized cystic lesion of the brain was controlled with the insertion of an Ommaya reservoir followed by the administration of stereotactic radiosurgery and chemotherapy, and the patient is currently doing well at 6 months, in comparison to the findings reported by others [3, 4], after the insertion of the device. Chemotherapy, as well as the insertion of the device, was also thought to have contributed the survival time of the patient, because the primary lesions and the metastasized lymph nodes were reduced after the administration of four cycles of carboplatin and pemetrexed.

Brain metastases are common in lung cancer patients, with an incidence of approximately 40 %. The majority of brain metastases of NSCLC are solid, whereas cystic brain metastases are exceedingly rare. While solid brain metastases are treated with optimal treatment modalities such as WBI, SRS or neurological surgery depending on the size and number of the metastases and the general conditions of the patient, cystic counterparts are generally resistant to radiation therapy, and neurosurgery of cystic lesions has been reported to be preferable to SRS or stereotactic aspiration when possible [5]. However, in the present case, due to the presence of multiple metastatic lesions, WBI was first chosen followed by insertion of an Ommaya reservoir for less invasiveness and to achieve ventricular drainage and drainage of the primary brain cystic tumors [1]. It is of note that no punctures were needed to drain the cystic tumors, as several punctures are generally required since the effusion typically fills the mass [3]. This may have been due to the reduction of viable cancer cells in the cystic wall by the multimodal treatments. Additionally,

although few complications are associated with the placement of the device, attention should be paid to potential adverse events caused by chemotherapy, including leucopenia, neutropenia and thrombocytopenia by chemotherapy, which can lead to critical complications such as intracranial hemorrhage or infection.

In conclusion, the insertion of an Ommaya reservoir is therefore considered to be a useful treatment modality to improve the neurological symptoms and PS in NSCLC patients with cystic brain metastasis with minimal invasiveness, thus allowing for the administration of further neurosurgical therapy and chemotherapy which are crucial for the successful treatment of advanced NSCLC.

Conflict of interest No authors have any conflict of interest to disclose.

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Renal Toxicity Caused by Brand-name Versus Generic Cisplatin: A Comparative Analysis

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Objective: A generic cisplatin formulation has replaced the brand-name formulation since November 2003 in our hospital. We retrospectively assessed the renal toxicity caused by the brand-name and generic cisplatin formulations.
Methods: The medical records of patients with thoracic malignancy who were treated at our hospital between November 2000 and April 2008 were reviewed. In total, 1296 eligible patients received 80 mg/m^2 of cisplatin: 499 patients were treated with the brand-name cisplatin formulation before November 2003 (Group 1) and 797 patients were treated with the generic formulation after November 2003 (Group 2). We compared the maximum serum creatinine level after chemotherapy in the two groups.
Results: The patient characteristics, including age, sex and performance status, and pretreatment serum creatinine levels were well balanced between the two groups. More patients received four cycles of chemotherapy in Group 2 ($P < 0.0001$). The median (range) of the maximum serum creatinine levels during all the chemotherapy cycles were 1.1 (0.5–4.1) mg/dl and 1.1 (0.5–4.4) mg/dl in Groups 1 and 2, respectively ($P = 0.0237$). The incidence of grade 0 serum creatinine elevations decreased from 47% to 39%, while that of grade 1 serum creatinine elevations increased from 32% to 41% ($P = 0.0094$). The incidence rates of grade 2 or 3 serum creatinine elevations were similar (21 vs. 20%). The time to serum creatinine elevation was also similar in Groups 1 and 2 ($P = 0.161$).
Conclusion: Although grade 1 maximum serum creatinine level was more common in the generic cisplatin formulation group, this was attributed to the larger number of patients receiving four cycles of chemotherapy in this group.

Key words: cisplatin – generic – brand name – renal toxicity

INTRODUCTION

Cisplatin-based chemotherapy is curative for testicular cancer and is active against gynecologic, gastrointestinal, genitourinary, head and neck, and lung cancers as well as other malignant diseases. Carboplatin has the same range of clinical activity as cisplatin but is less nephrotoxic and less emetogenic. Therefore, carboplatin has essentially replaced cisplatin for the treatment of ovarian cancer, lung cancer and a range of other malignancies (1). In some diseases, such as germ cell tumors (2), head and neck cancer (3), and non-small-cell lung cancer (4,5), however, cisplatin is more effective clinically in terms of the response rate and survival.

Cisplatin can cause dose-dependent renal toxicity. Large infusion amounts are needed to prevent cisplatin-induced renal toxicity. Patients are usually prehydrated and posthydrated with at least 2 l of IV fluid to maintain good urine flow. Risk factors for cisplatin nephrotoxicity include the dose and frequency of administration and the cumulative dose of cisplatin, older age, female sex, smoking and hypoalbuminemia (6).

Generic drugs are believed to be bioequivalent to brand-name drugs in terms of dosage form, safety, quality, performance and intended use. They are usually sold at substantial discounts from the branded price. The spread of generic drugs relieves the financial burden of patients' and improves the financial affairs of medical insurance providers (7). Recently, a retrospective analysis from the National Cancer Center Hospital (NCCH) in Tokyo, Japan, demonstrated that renal toxicity was more severe in patients treated with a generic cisplatin formulation than in those treated with the brand-name formulation, especially among male patients (8). To validate these findings, we conducted the same analysis in another patient cohort from the NCCH East, since the same generic cisplatin formulation had been introduced at our hospital, replacing the brand-name formulation, in November 2003.

PATIENTS AND METHODS

Patients were retrospectively selected for this study according to the following criteria, which were identical to those used in the previous analysis (8): (i) a histological or cytological diagnosis of thoracic malignancy; (ii) no prior chemotherapy; (iii) chemotherapy with a regimen that included 80 mg/m^2 of cisplatin; and (iv) receiving treatment as an inpatient at the NCCH East between November 2000 and April 2008. During this period the brand-name cisplatin formulation was administered between November 2000 and October 2003, and CISPLATIN for I.V. infusion (MARUKO), a generic cisplatin formulation, was administered thereafter. Patients with an abnormally elevated serum creatinine (CRN) level prior to the initiation of chemotherapy were excluded from this study. Serum CRN was measured using an enzymatic assay throughout the study period. The upper limit of normal for serum CRN was 1.1 mg/dl for men and 0.9 mg/dl for women.

After 750 ml of intravenous infusion fluids, cisplatin (80 mg/m^2) and 300 ml of fluids were intravenously infused over a 60-min period on day 1 in combination with other chemotherapeutic agents, followed by 40 g of mannitol and 1450 ml of hydration. A total of 2500 ml of hydration fluids, which consisted of 1000 ml of normal saline and 1500 ml of hypotonic crystalloid solution (Solita-T3®), were infused at a rate of 300 ml/h. Twenty milligrams of furosemide was intravenously administered at the end of hydration. One thousand milliliters of intravenous infusion fluids were administered on days 2 and 3 and 500 ml was administered on days 4 and 5 at a rate of 300 ml/h. Antiemetic prophylaxis consisted of a 5HT3 antagonist and 16 mg of dexamethasone on day 1, followed by 8 mg of dexamethasone on days 2 and 3 and 4 mg on days 4 and 5. This sequence of administration was consistently maintained during the study period.

The patients' baseline characteristics including age, sex, performance status (PS), pretreatment CRN level (CRN_{pre}), chemotherapy regimen, number of chemotherapy cycles and maximum CRN level (CRN_{max}) during the first cycle and during all chemotherapy cycles were retrospectively obtained from the patients' medical records. The median CRN_{max} and the Common Toxicity Criteria-Adverse Event (CTC-AE version 3.0) grades of the CRN_{max} were compared in patients treated with the brand-name cisplatin formulation (Group 1) and those treated with the generic formulation (Group 2). The time to serum CRN elevation was defined as the interval between the start of chemotherapy and the development of serum CRN elevation grade 1 or worse. Patients who did not develop serum CRN elevation grade 1 or worse were censored at the end of the cisplatin-based chemotherapy. The time to serum CRN elevation was estimated using the Kaplan–Meier analysis method (9) and was compared between groups using a log-rank test. Mann–Whitney tests were used to evaluate continuous variables and χ^2 tests were used for categorical variables. Multivariate analyses were performed using Cox proportional hazards models to determine the risk factors for the time until serum CRN elevation. Group 1 or 2 and the presence of significant risk factors in the univariate analyses were evaluated using a multivariate analysis. All the reported P values were two-sided. GraphPad InStat version 3.10 for Windows (GraphPad Software, San Diego, USA) and PASW Statistics 18 for Windows (SPSS Inc., Chicago, USA) were used for the statistical analyses. The present study was approved by an institutional review board.

RESULTS

Out of 1341 patients assessed for eligibility in this study, 1310 patients met the inclusion criteria; 31 patients were subsequently excluded because of an abnormal CRN_{pre} level. An additional 14 patients were excluded because they were treated with the brand-name cisplatin formulation during the first cycle of chemotherapy but received the generic formulation in subsequent cycles. Therefore, a total of 1296 patients were eligible for this analysis. In total, 499 patients were treated with the brand-name cisplatin formulation (Group 1) and 797 patients were treated with the generic formulation (Group 2) (Fig. 1). The patient characteristics are shown in Table 1. The median age was 63 years (range 27–81 years), and the female patients accounted for 23% of all the patients. No statistical differences in sex, age, PS or CRN_{pre} were observed between the two groups. The most common chemotherapy regimen was cisplatin plus vinorelbine; however, this regimen was less frequently used in Group 2, whereas cisplatin plus gemcitabine was more frequently used. The median number of chemotherapy cycles was three in both groups, but more patients received four cycles of chemotherapy in Group 2 (Fig. 2).

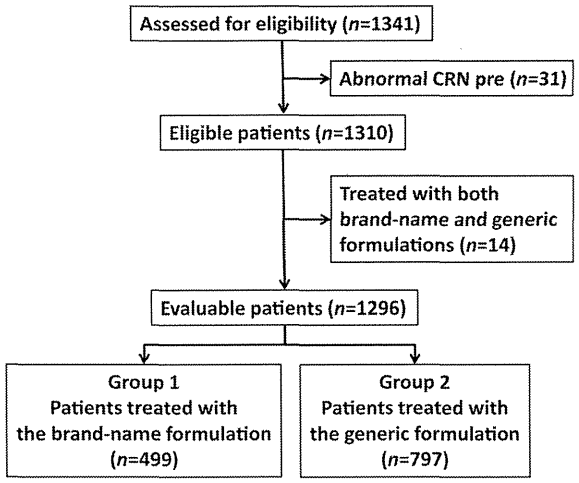

Figure 1. Diagram of the study. CRN_{pre}, pretreatment serum creatinine level.

Table 1. Patient characteristics

	Group 1[a] ($n = 499$), N (%)	Group 2[b] ($n = 797$), N (%)	P value
Sex			
Male	392 (79)	611 (77)	0.4532
Female	107 (21)	186 (23)	
Age (years)			
Median (range)	62 (28–78)	63 (27–81)	0.7368
Performance status			
0–1	486 (97)	788 (99)	0.0744
2–3	13 (3)	9 (1)	
Pretreatment serum creatinine level			
Median (range)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.1742
Regimen of chemotherapy			
CDDP + VNR	356 (71)	447 (56)	<0.0001
CDDP + ETP	57 (12)	121 (15)	
CDDP + GEM	36 (7)	149 (19)	
CDDP + others	50 (10)	80 (10)	
Number of cycles			
1	53 (11)	72 (9)	<0.0001
2	187 (37)	184 (23)	
3	136 (27)	241 (30)	
4	114 (23)	294 (37)	
5	3 (1)	1 (0)	
6	6 (1)	5 (1)	
Median (range)	3 (1–6)	3 (1–6)	<0.0001

CDDP, cisplatin; VNR, vinorelbine; GEM, gemcitabine; others included irinotecan, docetaxel, vinorelbine + mitomycin C, paclitaxel and S-1.
[a]Patients treated with the brand-name cisplatin formulation.
[b]Patients treated with a generic cisplatin formulation

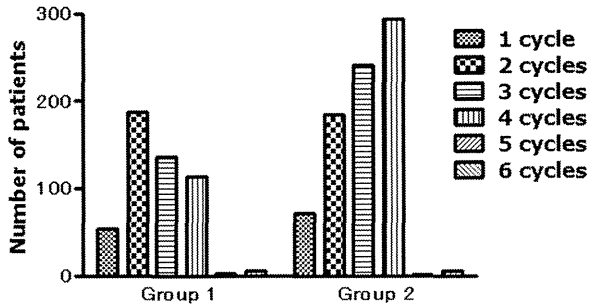

Figure 2. Number of chemotherapy cycles in 499 patients treated with the brand-name cisplatin formulation (Group 1) and 797 patients treated with the generic formulation (Group 2).

The median (range) CRN_{max} levels during the first cycle of chemotherapy were 1.0 (0.5–4.1) mg/dl and 1.0 (0.6–4.2) mg/dl in the male patients in Groups 1 and 2, respectively ($P = 0.0378$), whereas they were 0.7 (0.5–1.8) mg/dl and 0.7 (0.4–1.9) mg/dl in the female patients in Groups 1 and 2, respectively ($P = 0.3949$). The CTC-AE grade for CRN_{max} during the first cycle was not statistically different between Groups 1 and 2 in both male ($P = 0.6732$) and female patients ($P = 0.9518$) (Table 2).

The median (range) CRN_{max} levels during all the chemotherapy cycles were 1.1 (0.5–4.1) mg/dl and 1.1 (0.5–4.4) mg/dl in all the patients in Groups 1 and 2, respectively ($P = 0.0237$). The median (range) CRN_{max} levels during all the cycles of chemotherapy were 1.2 (0.5–4.1) mg/dl and 1.2 (0.6–4.4) mg/dl in the male patients in Groups 1 and 2, respectively ($P = 0.0029$), whereas they were 0.8 (0.5–2.6) mg/dl and 0.9 (0.5–2.2) mg/dl in the female patients in Groups 1 and 2, respectively ($P = 0.3745$). The CTC-AE grade for CRN_{max} during all the cycles was statistically different between Groups 1 and 2 in the male patients ($P = 0.0431$). Grade 0 CRN_{max} decreased from 49% to 42%, whereas grade 1 CRN_{max} increased from 32% to 41% between the male patients in Groups 1 and 2. An identical tendency was observed in the female patients. Grade 0 CRN_{max} decreased from 39% to 31%, whereas grade 1 CRN_{max} increased from 31% to 41% between the female patients in Groups 1 and 2 ($P = 0.1455$). In all the patients, grade 0 CRN_{max} decreased from 47% to 39% and grade 1 CRN_{max} increased from 32% to 41% between Groups 1 and 2 ($P = 0.0094$). Grade 2 or 3 CRN_{max} was not different between Groups 1 and 2 in both the male and female patients (Table 3). The time to serum CRN elevation was not statistically different between Groups 1 and 2 ($P = 0.161$) (Fig. 3). A male sex or an age of 71 years or older was significantly associated with a shorter time to a serum CRN elevation grade 1 or worse in a univariate analysis (Table 4).

A multivariate analysis showed that a female sex [hazard ratio (HR): 1.528, 95% confidence interval (CI): 1.296–1.803] and an age of 71 years or older (HR: 1.362, 95% CI: 1.127–1.645) were significant risk factors for the time to serum CRN elevation. Group 2 was not a significant risk

Table 2. Serum creatinine levels and toxicity grades during the first cycle of chemotherapy

	Group 1[a] ($n = 499$), N (%)	Group 2[b] ($n = 797$), N (%)	P value
Median (range)			
Total	0.9 (0.5–4.1)	0.9 (0.4–4.2)	0.1269
Male	1.0 (0.5–4.1)	1.0 (0.6–4.2)	0.0378
Female	0.7 (0.5–1.8)	0.7 (0.4–1.9)	0.3949
CTC-AE grade			
Total			
0	339 (68)	514 (64)	0.6244
1	123 (24)	218 (27)	
2	34 (7)	61 (8)	
3	3 (1)	4 (1)	
Male			
0	282 (72)	418 (68)	0.6732
1	83 (21)	147 (24)	
2	24 (6)	42 (7)	
3	3 (1)	4 (1)	
Female			
0	57 (53)	96 (52)	0.9518
1	40 (38)	71 (38)	
2	10 (9)	19 (10)	

CTC-AE, Common Toxicity Criteria-Adverse Event Ver. 3.0.
[a]Patients treated with the brand-name formulation.
[b]Patients treated with a generic formulation.

Table 3. Serum creatinine levels and toxicity grades during all cycles of chemotherapy

	Group 1[a] ($n = 499$), N (%)	Group 2[b] ($n = 797$), N (%)	P value
Median (range)			
Total	1.1 (0.5–4.1)	1.1 (0.5–4.4)	0.0237
Male	1.2 (0.5–4.1)	1.2 (0.6–4.4)	0.0029
Female	0.8 (0.5–2.6)	0.9 (0.5–2.2)	0.3745
CTC-AE grade			
Total			
0	236 (47)	314 (39)	0.0094
1	159 (32)	326 (41)	
2	100 (20)	150 (19)	
3	4 (1)	7 (1)	
Male			
0	194 (49)	256 (42)	0.0431
1	126 (32)	249 (41)	
2	69 (18)	100 (16)	
3	3 (1)	6 (1)	
Female			
0	42 (39)	58 (31)	0.1455
1	33 (31)	77 (41)	
2	31 (29)	50 (27)	
3	1 (1)	7 (1)	

[a]Patients treated with the brand-name cisplatin formulation.
[b]Patients treated with a generic cisplatin formulation.

factor for the time to serum CRN elevation (HR: 1.096, 95% CI: 0.943–1.276) (Table 5).

DISCUSSION

A previous retrospective analysis from the NCCH in Tokyo, Japan, demonstrated that a grade 2 or 3 CRN_{max} was observed in 9.4% of the male patients treated with the brand-name cisplatin formulation and 20.9% of the male patients treated with a generic formulation identical to that used in our study during all the chemotherapy cycles ($P < 0.001$) (8). In our study, grade 2 or 3 CRN_{max} was observed in 19 and 17% of the male patients of the two groups, respectively. Three thousand milliliters on day 1 and 2000 ml of intravenous infusion fluids on days 2–5 were administered at the NCCH, with identical antiemetic prophylaxis of a 5HT3 antagonist and dexamethasone and 40 g of mannitol on day 1. However, 2,500 ml of intravenous infusion fluids on day 1, 1000 ml on days 2 and 3, and 500 ml on days 4 and 5 were administered in our hospital. The median age of patients was 60 years in the NCCH study and 63 years in this study. The reason why our study could not confirm a

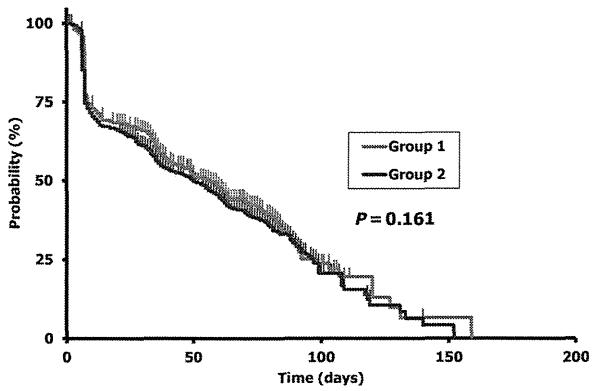

Figure 3. Kaplan–Meier curves for time to serum creatinine elevation. The patients in Group 1 were treated with the brand-name cisplatin formulation, while the patients in Group 2 were treated with the generic formulation. The probability means the percentage of patients who did not develop elevation of the serum creatinine level. Patients who did not develop serum creatinine elevation grade 1 or worse were censored at the end of the cisplatin-based chemotherapy. Therefore, these Kaplan–Meier curves reveal when serum creatinine elevated after the initiation of cisplatin-based chemotherapy.

Table 4. Time to serum creatinine elevation grade 1 or worse (univariate analysis)

	Median time to serum creatinine elevation (days)	95% confidence interval	*P* value
Gender			
Male	60	53.7–66.3	<0.001
Female	29	21.5–36.5	
Age			
≤70 years old	56	49.9–62.1	0.003
≥71 years old	34	19.4–48.6	
Cisplatin group			
Group 1	56	46.1–65.9	0.161
Group 2	50	42.0–58.0	

Patients in Group 1 were treated with the brand-name cisplatin formulation, whereas patients in Group 2 were treated with a generic cisplatin formulation.

Table 5. Multivariate analysis of risk factors associated with time to serum creatinine elevation.

Variable	Hazard ratio	95% confidence interval	*P*-value
Female sex	1.528	1.296–1.803	<0.001
Age ≥71 years old	1.362	1.127–1.645	0.001
Group 2	1.096	0.943–1.276	0.229

Patients in Group 2 were treated with a generic cisplatin formulation.

high frequency of grade 2–3 CRN_{max} in the generic cisplatin formulation group is unknown. Although grade 1 CRN_{max} was more common in the generic cisplatin formulation group, this was attributed to the larger number of patients receiving four cycles of chemotherapy in this group. A multivariate analysis also demonstrated that the generic cisplatin formulation group was not a statistically significant risk factor associated with the time to serum CRN elevation. We concluded that the generic cisplatin formulation did not increase renal toxicity compared with the brand-name cisplatin formulation.

The main objective of using generic drugs, rather than the brand-name drugs, is cost savings (10). Generic drugs are usually approved without clinical trials, although the same high quality, strength, purity and stability as brand-name drugs are required. Our study suggested that the generic cisplatin formulation did not increase renal toxicity, compared with the brand-name formulation. This kind of survey is needed for other generic drugs, especially anticancer drugs that can cause severe or life-threatening toxicities. We believe it is important to confirm the safety of generic drugs. If possible, it is desirable to conduct clinical trials to evaluate the safety and efficacy of generic drugs before approval. However, a large-scale clinical trial needs great cost and is impracticable to conduct.

Magnesium was not included in the hydration fluid. Several randomized trials have demonstrated that the addition of magnesium is effective for reducing cisplatin-induced renal toxicity (11,12). Grade 2–3 CRN_{max} was observed in ~20% of patients, which sounds still high. A four-arm cooperative study in Japan demonstrated that the incidence of grade 2–3 serum CRN elevation was 7–9% in the cisplatin-based chemotherapy group (13). We analyzed consecutive patients who were treated with cisplatin-based chemotherapy; therefore, more patients who had co-morbidity and were ineligible for clinical trials might have been included in this study, resulting in a higher incidence of grade 2–3 serum CRN elevation than those in clinical trials. To reduce cisplatin-induced renal toxicity, we have added magnesium to the hydration fluid administered prior to cisplatin since 2010. We plan to analyze whether preloading with magnesium before chemotherapy can further reduce cisplatin-induced renal toxicity.

Our retrospective analysis has several limitations. First, other risk factors for cisplatin nephrotoxicity, such as smoking status, pretreatment serum albumin level or the co-administration of non-steroidal anti-inflammatory agents, were not investigated. Secondly, aprepitant, which is a standard antiemetic agent nowadays (14), was approved in late 2009 in Japan. None of the patients in our study received aprepitant. The introduction of aprepitant might reduce anorexia induced by cisplatin and might prevent dehydration and renal dysfunction. Thirdly, the frequency of chemotherapy delay, dose reduction or termination of chemotherapy due to renal toxicity was not investigated. This information will be helpful to understand the clinical impact of the renal toxicity.

In conclusion, the incidence of grade 2–3 CRN_{max} was not higher in the generic cisplatin group, although the incidence of grade 1 CRN_{max} was higher. However, more patients in the generic cisplatin formulation group received four cycles of chemotherapy than in the brand-name cisplatin group. The time to serum CRN elevation was not statistically different between the two groups.

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Conflict of interest statement

None declared.

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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

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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

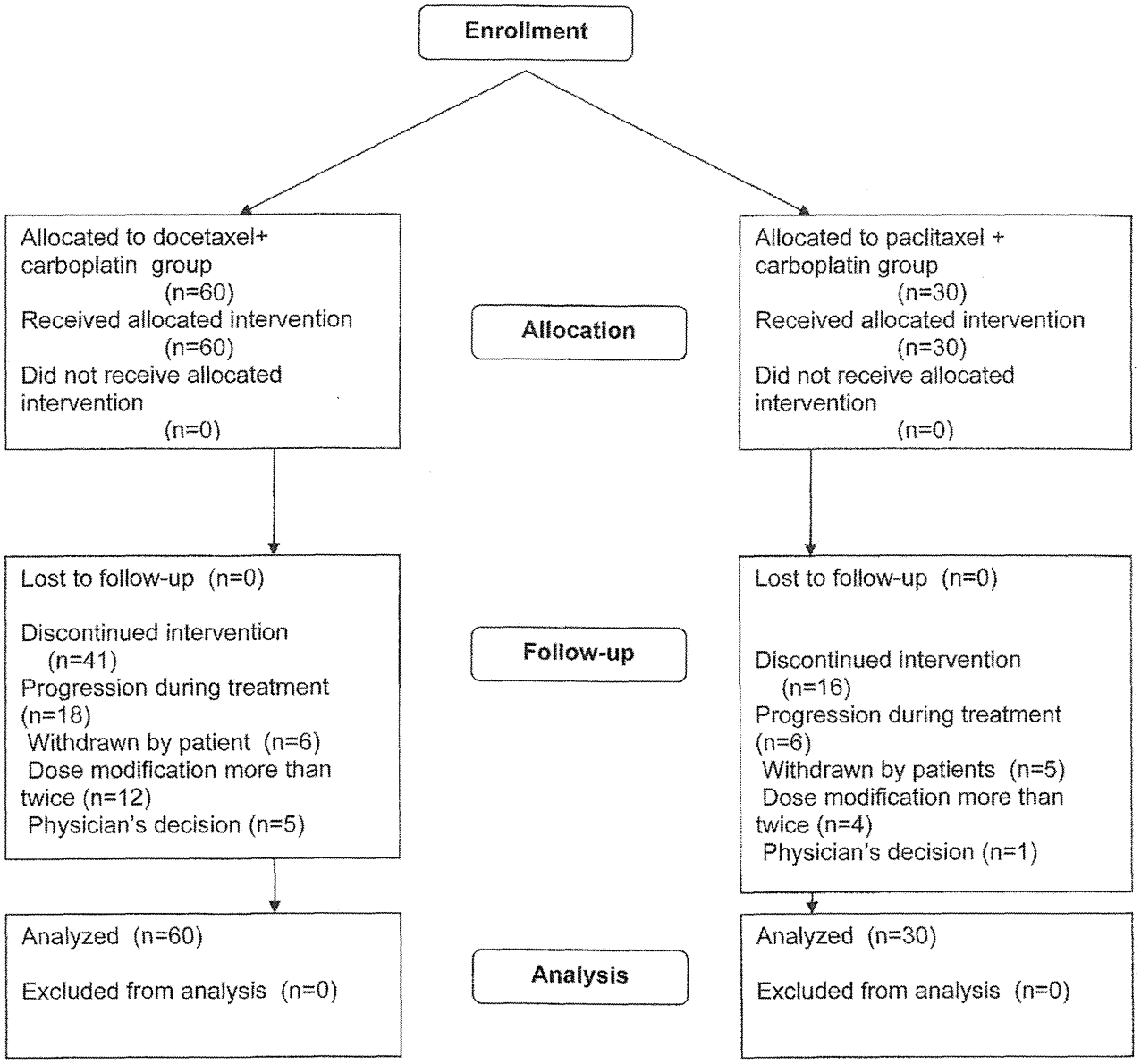

Figure 1. *Study design and patient flow. n: Number of patients.*

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