

## **Phase I Study of Carboplatin Combined with Pemetrexed for Elderly Patients with Advanced Non-squamous Non-small Cell Lung Cancer**

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## **Abstract**

**Introduction:** The primary objective of this study was to evaluate the safety and tolerability of carboplatin plus pemetrexed for elderly patients ( $\geq 75$  years) with chemotherapy-naïve advanced non-squamous (non-sq) non-small cell lung cancer (NSCLC).

**Methods:** Patients received escalated doses of carboplatin at an area under the concentration-time curve (AUC) of 4 (level 1) or 5 (level 2) plus pemetrexed (500 mg/m<sup>2</sup>) every 3 weeks for a maximum of 6 cycles. Dose escalation was decided according to whether dose-limiting toxicity (DLT) occurred in the first cycle of chemotherapy.

**Results:** A total of 20 patients (6 at level 1, 14 at level 2) were enrolled. No DLTs were observed in patients at level 1 or the first 6 patients at level 2, and therefore the combination of carboplatin at an AUC of 5 plus pemetrexed at 500 mg/m<sup>2</sup> was considered to be the recommended dose. Among a total of 14 patients in level 2, only one patient experienced DLT: grade 3 febrile neutropenia and urticaria. The major toxicities were neutropenia, thrombocytopenia, and anemia. Liver dysfunction, fatigue, and anorexia were also common, but generally manageable. Six patients showed partial responses, giving the overall response rate of 30%. The median progression-free survival period was 4.8 months (95% CI 2.9-6.7 months).

**Conclusions:** The combination of carboplatin at an AUC of 5 plus pemetrexed at 500 mg/m<sup>2</sup> was determined as the recommended dose in chemotherapy-naïve elderly patients ( $\geq 75$  years) with advanced non-sq NSCLC, in view of overall safety and tolerability.

## Mini-abstract

The combination of carboplatin at an AUC of 5 plus pemetrexed at 500 mg/m<sup>2</sup> was determined as the recommended dose in chemotherapy-naïve elderly patients ( $\geq 75$  years) with advanced non-sq NSCLC.

## Introduction

Lung cancer is the leading cause of cancer death worldwide. Approximately 85% of lung cancers are non-small cell types, and approximately 70% of patients with non-small-cell lung cancer (NSCLC) already have inoperable, locally advanced or metastatic disease at diagnosis (1). As society ages, the ratio of elderly lung cancer patients older than 75 years has increased significantly in the lung cancer patient population as a whole (2, 3). Platinum-doublet chemotherapies have been established as the standard for advanced NSCLC (4-6). However, their efficacy for elderly patients has been under-represented in clinical trials, and therefore their role in this setting is still not clear.

Previously, some prospective randomized controlled trials for elderly NSCLC patients have investigated the optimal forms of chemotherapy for them. The ELVIS trial (7) demonstrated that treatment with vinorelbine resulted in better survival and quality of life than best supportive care, and another group reported that docetaxel improved progression-free survival (PFS), response rate, and disease-related symptoms in comparison with vinorelbine (8). Based on these results, the current standard treatment for elderly patients with advanced NSCLC is still monotherapy, such as docetaxel or vinorelbine. However, subset analyses in some phase III trials have reported that platinum-doublet chemotherapies may be feasible and promising for fit elderly patients with good performance status (PS) and adequate organ function (9, 10). Recently, a phase III trial for elderly patients ( $\geq 70$  years) with NSCLC comparing the carboplatin-paclitaxel combination with monotherapy, such as gemcitabine or vinorelbine (IFCT 0501), demonstrated that platinum-doublet chemotherapy yielded better survival than monotherapy. Although the toxicities of platinum-doublet

chemotherapy are indeed higher, this approach may be promising for elderly NSCLC patients (11).

Pemetrexed is a multitargeting anti-folate chemotherapeutic agent reported to be as effective as docetaxel in a second-line setting, with less toxicity (12). Furthermore, cisplatin in combination with pemetrexed is now considered to be the standard first-line regimen for non-squamous (non-sq) NSCLC based on the results of a previous phase III trial (13). Because carboplatin-based regimens have been shown to be less toxic, more convenient, they have been widely used as a substitute for cisplatin regimens in clinical practice, especially for elderly patients. In a previous dose escalation study of carboplatin plus pemetrexed for patients aged <75 years with advanced NSCLC, this combination was shown to be effective and less toxic (14). However, the optimal doses of carboplatin and pemetrexed for patients aged  $\geq 75$  years with advanced non-sq NSCLC have not yet been fully evaluated. Therefore, we conducted the present prospective study to evaluate the safety and tolerability of this combination therapy for elderly patients ( $\geq 75$  years) with chemotherapy-naïve advanced non-sq NSCLC.

## Patients and Methods

### Study Design

This was a dose escalation study of carboplatin in combination with pemetrexed for elderly patients aged  $\geq 75$  years with chemotherapy-naïve advanced non-sq NSCLC. The primary objectives were to estimate the maximum tolerable dose (MTD) and determine the recommended dose (RD). The secondary objectives were to determine the response rate, PFS, overall survival (OS), and toxicity profiles.

This study consisted of two parts. Part 1 was the dose escalation phase, and Part 2 was the expansion phase. In Part 1, 6 patients were treated with carboplatin at an area under the concentration-time curve (AUC) of 4 plus pemetrexed at 500 mg/m<sup>2</sup> (level 1). If 4 of these 6 patients experienced dose-limiting toxicity (DLT), the study was terminated. If 3 of the patients or fewer experienced DLT, dose escalation was continued to the next level. At dose level 2, 6 patients received carboplatin at an AUC of 5 plus 500 mg/m<sup>2</sup> pemetrexed. If 4 of them experienced DLT, this level was considered to be the MTD, and the study was moved to Part 2 at dose level 1. If DLT was observed in 3 of 6 patients or fewer, the study was moved to Part 2 at dose level 2. In Part 2, additional patients, up to a maximum of 14, were enrolled to receive carboplatin plus pemetrexed at the doses determined in Part 1. Although dose escalation was decided according to whether DLT occurred only in the first cycle of chemotherapy, RD was finally decided according to the toxicities observed throughout all of the treatment periods.

### Eligibility

Patients with histologically or cytologically confirmed non-sq NSCLC were eligible for this study. Each of the patients were required to meet the following criteria: (1) clinical stage III (not amenable to radiotherapy), IV, or postoperative recurrence; (2) age 75 years or older; (3) measurable lesions on the basis of Response Evaluated Criteria in Solid Tumors (RECIST) ver1.0; (4) Eastern Cooperative Oncology Group (ECOG) PS of 0-1; (5) no prior chemotherapy for NSCLC, with the following minimum intervals since previous treatment:  $\geq 4$  weeks after surgery, and  $\geq 4$  weeks after curative thoracic irradiation or  $\geq 2$  weeks after the last irradiation to other organs; (6) adequate organ function {white blood cell count (WBC)  $\geq 4000/\text{mm}^3$ , neutrophil count  $\geq 2000/\text{mm}^3$ , hemoglobin  $\geq 9.0$  g/dl, platelet count  $\geq 100,000/\text{mm}^3$ , serum creatinine  $\leq 1.5$  mg/dl, creatinine clearance  $\geq 45$  ml/min, serum total bilirubin  $\leq 1.5$  mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 100$  U/l, partial pressure of arterial oxygen (PaO<sub>2</sub>)  $\geq 70$  mmHg (on room air)}; (7) life expectancy  $\geq 3$  months.

This study was approved by the institutional review board at Kurume University before commencement. All patients provided written informed consent before the start of study treatments. This study was registered with UMIN (University Hospital Medical Information Network in Japan), number UMIN 000003231.

### Study treatment

All patients received 500 mg/m<sup>2</sup> pemetrexed by intravenous infusion within 10 minutes, followed by intravenous infusion of carboplatin over at least 30 minutes (to give an AUC of 4 or 5) on day 1 of the 21-day cycle. Carboplatin doses were determined using the estimated creatinine clearance (Cockcroft-Gault formula) and the Calvert formula based on AUC. Standard antiemetic prophylaxis with intravenous 5-hydroxytryptamine-3 antagonist and dexamethasone was administered before chemotherapy. Combination chemotherapy was repeated every 3 weeks for a maximum of 6 cycles. Subsequent cycles of chemotherapy were withheld until the following criteria were satisfied: WBC >3000/mm<sup>3</sup> or neutrophil count >1500/mm<sup>3</sup>, platelet count ≥100000/mm<sup>3</sup>, PS ≤1, SpO<sub>2</sub> ≥95%, AST/ALT ≤100 U/l, total bilirubin ≤1.5 mg/dl, serum creatinine ≤1.5 mg/dl, other non-hematological toxicity ≤grade 1. If these criteria were unsatisfied within 43 days from day 1 of the current cycle, the patient was excluded from further participation. The carboplatin and pemetrexed doses were to be reduced from dose level 2 to level 1, or from dose level 1 to an AUC of 4 and 400 mg/m<sup>2</sup>, respectively, in the subsequent cycle if toxicity equivalent to DLT occurred. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was not allowed at any time during the study.

While the patients were being studied, they received supplementary folic acid and vitamin B12. All patients underwent comprehensive baseline assessments including clinical laboratory tests and imaging studies. Patients also received follow-up assessments and monitoring at regular intervals. Toxicity evaluations were based on the Common Terminology Criteria for Adverse Events, version 3.0.

### Definition of DLT

DLT was defined as a toxicity occurring in cycle 1 that met one of the following criteria and for which a causal relationship with carboplatin or pemetrexed could not be ruled out: (1) grade 4 neutropenia lasting 5 days or longer; (2) febrile neutropenia; (3) grade 4 thrombocytopenia, grade 3 thrombocytopenia that required platelet transfusion or was associated with bleeding; (4) grade 3 or 4 non-hematological toxicity (the

following events were to be regarded as DLT if they did not recover to  $\leq$  grade 2 despite standard/optimal supportive treatment: nausea, vomiting, anorexia, fatigue, constipation, diarrhea, or transient electrolyte abnormality). If the patients experienced toxicities that met the DLT criteria, the treatment doses were modified in subsequent courses

#### Safety and efficacy evaluation

All patients who received at least one dose of the study treatment were included in the safety and efficacy analysis. A maximum of 20 patients were to be enrolled in this study to evaluate the safety of the carboplatin and pemetrexed combination. At least 14 patients were to be treated at the recommended doses. The probability of adverse events with incidences equal to or greater than 20% not being detected in any of the 14 patients was 4.4%.

The efficacy endpoints were tumor response, PFS and OS. Tumor response was evaluated according to the RECIST guidelines (15). PFS was defined as the period from enrollment to the date of confirmation of progressive disease (PD) or the date of death due to any cause, whichever was earlier. OS was defined as the period from registration until death due to any cause. Patients not known to have died or to have suffered progression were censored at the date of the last progression-free assessment. The survival data were cut-off by June 2013.

#### Statistical analyses

The Kaplan-Meier (K-M) method was used for PFS and OS analysis. This included generation of the K-M curve and determining the median with the 95% confidence interval. The incidence of adverse events was calculated for each dose group. The distribution of best overall response was summarized in the patients who had target lesions

## Results

### Patient characteristics

Between March 2010 and November 2012, 20 patients were enrolled into this study at Kurume University Hospital. The patients' characteristics are listed in Table 1. The median age was 77 years (range, 75 to 83 years), 13 patients were male and 7 were female, and 14 patients (70%) had PS 0-1. All patients had adenocarcinoma histology. Epidermal growth factor receptor (EGFR) mutation status was examined in 17 patients. Four patients had EGFR mutation (1 had exon 19 deletions, and 3 had a L858R missense mutation in exon 21). Nine of these patients had a previous treatment history such as pleurodesis, palliative radiotherapy including whole-brain irradiation, gamma-knife, and curative thoracic radiotherapy.

### Determination of recommended dose

The profiles of the major toxicities observed in cycle 1 are shown in Table 2. In Part 1, no DLT was observed in 6 patients at dose level 1. The dose of carboplatin and pemetrexed was then escalated to level 2. At dose level 2, no DLT was also observed in 6 patients. Therefore, although the MTD had not been reached, the RD was assumed to be carboplatin at an AUC of 5 plus pemetrexed at 500 mg/m<sup>2</sup>, and an additional 8 patients were assigned to this dose level. In total, 14 patients received carboplatin at an AUC of 5 plus pemetrexed at 500 mg/m<sup>2</sup>. Among these 14 patients, only one patient experienced DLTs in cycle 1: grade 3 febrile neutropenia, urticaria and grade 4 thrombocytopenia.

### Treatment delivery

At dose level 1, for 6 patients who received carboplatin at an AUC of 4 and pemetrexed at 500 mg/m<sup>2</sup>, a total of 23 cycles of combination therapy were delivered overall. The median number of cycles was 4 (range 2-6). Two of those patients required dose reduction due to adverse events (AEs) in 2 cycles (9% of the total cycles). At level 2, for 14 patients who received carboplatin at an AUC of 5 and pemetrexed at 500 mg/m<sup>2</sup>, a total of 48 cycles of combination therapy were delivered overall. The median number of cycles was 4 (range 1-6). Four of those patients required dose reduction due



to AEs in 5 cycles (10% of the total cycles) and dose delays in 2 cycles (4% of the total cycles). One patient required dose reduction twice due to AEs. Four patients discontinued the study protocol because of AEs (2 due to dose delay after thrombocytopenia, one at the investigator's discretion related to AEs, and patient refusal related to AEs, respectively). The major reasons for dose reductions and dose delays were hematologic toxicities. The average treatment interval was 25 days.

### Toxicities

The profiles of major toxicities and severe toxicities observed during the entire treatment period are shown in Tables 3. All patients (n=20) who received combination therapy were assessable for toxicity. The most frequent grade 3 or 4 toxicity was hematologic toxicities. Such toxicities  $\geq$  grade 3 were neutropenia (55%), anemia (40%), thrombocytopenia (40%), and leukopenia (40%). Of these events, grade 4 thrombocytopenia and grade 3 or 4 anemia were observed in 4 and 8 patients, respectively. Among them, transfusion of platelets and red blood cells was performed in 2 and 5 patients, respectively, throughout the entire study period. G-CSF was administered in only one patient who developed febrile neutropenia (a DLT case). On the other hand, grade 3 or 4 non-hematological toxicities were febrile neutropenia (5%), anorexia (5%) and urticaria (5%). Although non-hematological toxicities were generally manageable with supportive care, dose delays or reductions, anorexia and fatigue tended to be more frequent than those in non-elderly patients reported previously. No treatment-related deaths occurred in this study.

### Efficacy

The efficacy data are shown in Table 4. Among 20 evaluable patients, 6 had partial responses (1 patient at dose level 1 and 5 at dose level 2) and 9 had stable disease. The overall response rate was 30%, and the disease control rate was 75%. After a median follow-up period of 10.1 months (range, 1.3-28.2 months), 7 patients were still alive. The median PFS for the patients overall was 4.8 months (95% CI 2.9-6.7 months; fig.1), and the median OS was 17.8 months (95% CI 8.6-27.0 months; fig.2).

### Post-discontinuation chemotherapy

Among 18 patients who showed disease progression, 14 (77.8%) received second-line chemotherapy, and 4 received only best supportive care due to poor PS. All four patients who had EGFR mutation received gefitinib as second-line chemotherapy; the rest received docetaxel or erlotinib.

## Discussion

We conducted a prospective study to evaluate the safety and tolerability of combination chemotherapy with carboplatin and pemetrexed in elderly patients ( $\geq 75$  years) with chemotherapy-naïve advanced non-sq NSCLC. Six patients were treated with carboplatin at an AUC of 4 (level 1) and pemetrexed at 500 mg/m<sup>2</sup>, and 14 patients received carboplatin at an AUC of 5 (level 2) and pemetrexed at 500 mg/m<sup>2</sup>. Because we had originally planned not to escalate the doses exceeded at dose level 2, we accrued a further 8 patients at dose level 2 based on the protocol for Part 2 (expansion phase). In Part 2, DLT was observed in 1 patient in the first cycle, and as a result, only 1 out of 14 patients (7%) finally experienced DLT at dose level 2.

Next, we evaluated the adverse events of this combination therapy during all treatment periods, and found that the incidence of hematologic toxicities, especially thrombocytopenia and anemia, was markedly higher than expected. In this study, 6 (30%) of 20 patients required either platelet or red blood cell transfusion, and 2 (10%) were withdrawn from the study due to persistent thrombocytopenia. Although it is very difficult to predict the severity of hematological toxicities before the start of treatment, it is rare for transfusion to be necessary in the first cycle. With regard to non-hematologic toxicities, fatigue and anorexia seemed to be more frequent and prolonged than those in younger patients, although their grades were less than 2 and these events were well manageable with supportive care. A previous meta-analysis comparing single agents with platinum-doublet chemotherapy in elderly patients ( $\geq 70$  years) reported that use of platinum-doublet was associated with a higher incidence of grade 3 or 4 thrombocytopenia and anemia than was the case for single agents (16). The IFCT-0501 study comparing carboplatin-paclitaxel with single agents, such as gemcitabine or vinorelbine, also demonstrated that hematological toxicities were more frequent in the platinum-doublet chemotherapy group (11). Therefore, the toxicity profiles we obtained were consistent with these previous reports.

The overall response rate of 30%, the median PFS of 4.8 months (95% CI 2.9-6.7 months), and the median OS of 17.8 months (95% CI 8.6-27.0 months) were thought to be encouraging results. A previously reported dose escalation study conducted by another group in Japan demonstrated an overall response rate of 47.1%, a median PFS of 5.1 months (95% CI 2.4-7.7 months), and a median OS of 16.5 months (95% CI 7.7-26.9 months) (17). Furthermore, currently reported phase II study of carboplatin and pemetrexed for elderly patients ( $\geq 70$  years) yielded an overall response rate of 28.6%, a

median PFS of 5.5 months (95% CI 4.7-6.7 months), and a median OS of 10.4 months (95% CI 9.1-12.9 months) (18). Although these studies, and our present one, employed small sample sizes, they demonstrated an efficacy similar to that in younger patients, and therefore the combination of carboplatin and pemetrexed for elderly patients is thought to be worth further investigation.

For non-elderly patients, the recommended dose of this combination was carboplatin at an AUC of 6 and pemetrexed at 500 mg/m<sup>2</sup>, based on a previous dose escalation study (14). However, we did not plan to escalate that dose level in the present study for the following reasons: First, in the dose escalation study for non-elderly patients, hematological toxicities were more frequent for carboplatin at an AUC of 6 and pemetrexed at 500 mg/m<sup>2</sup> than for carboplatin at an AUC of 5 and pemetrexed at 500 mg/m<sup>2</sup>. Second, in the phase III study that compared carboplatin plus pemetrexed with carboplatin plus gemcitabine, which is one of the standard regimens for NSCLC, there was no significant inter-group difference in the OS, in spite of the fact that carboplatin was set at an AUC of 5 (19). In addition, we did not plan pemetrexed maintenance therapy from the outset because when we originally planned this study in 2009, the results of pemetrexed maintenance therapy had not been reported, although the usefulness of pemetrexed maintenance therapy had been demonstrated in some phase III studies (20, 21), and pemetrexed-based induction therapy followed by pemetrexed maintenance therapy is now a standard treatment for non-elderly patients with non-sq NSCLC. For elderly patients ( $\geq 75$  years), there are still no definitive data regarding maintenance therapy after platinum-doublet induction therapy, and therefore this type of maintenance therapy is also worth evaluating in the future.

On the other hand, patient selection is a very important issue in the elderly population, especially patients aged  $\geq 75$  years, because most such patients are thought to have a natural decline of physiological function and have a potential for more comorbidities or to be taking more concomitant medications than younger patients, although chronological age is not always an exact indicator of organ function. Recently, the Cancer-Specific Geriatric Assessment (CSGA) has been devised, and its usefulness reported (22-24), further investigations being ongoing. It is hoped that the CSGA will be a helpful tool for selection of fit elderly patients for chemotherapy.

In conclusion, the combination of carboplatin at an AUC of 5 plus pemetrexed at 500 mg/m<sup>2</sup> was determined as the recommended dose for chemotherapy-naïve elderly patients ( $\geq 75$  years) with advanced non-Sq NSCLC. Our findings provide some rationale for the ongoing randomized controlled trial comparing this regimen followed by pemetrexed maintenance therapy with docetaxel monotherapy in elderly patients

( $\geq 75$  years) with non-sq NSCLC (UMIN000011460).

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#### Conflicts of interest

The authors declare no conflicts of interest.

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