A randomized, open-label, phase III trial comparing amrubicin versus docetaxel in patients with previously treated non-small-cell lung cancer


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Background: Amrubicin is approved for treating non-small-cell lung cancer (NSCLC) and small-cell lung cancer. However, no direct comparisons between amrubicin and docetaxel, a standard treatment for NSCLC, have been reported.

Patients and methods: We conducted a randomized phase III trial of Japanese NSCLC patients after one or two chemotherapy regimens. Patients were randomized to amrubicin (35 mg/m² on days 1–3 every 3 weeks) or docetaxel (60 mg/m² on day 1 every 3 weeks). Outcomes included progression-free survival, overall survival, tumor responses, and safety.

Results: Between October 2010 and June 2012, 202 patients were enrolled across 32 institutions. Median progression-free survival (3.6 versus 3.0 months; P = 0.54) and overall survival (14.6 versus 13.5 months; P = 0.86) were comparable in the amrubicin and docetaxel groups, respectively. The overall response rate was 14.4% (14/97) and 19.6% (19/97) in the amrubicin and docetaxel groups, respectively (P = 0.45). The disease control rate was 55.7% in both groups. Adverse events occurred in all patients, and included grade ≥3 neutropenia occurred in 82.7% and 78.8% of patients in the amrubicin and docetaxel groups, respectively (P = 0.45). The disease control rate was 55.7% in both groups. Adverse events occurred in all patients, and included grade ≥3 neutropenia occurred in 82.7% and 78.8% of patients in the amrubicin and docetaxel groups, respectively, grade ≥3 leucopenia occurred in 63.3% and 70.7%, and grade ≥3 febrile neutropenia occurred in 13.3% and 18.2% of patients in the amrubicin and docetaxel groups, respectively. Of eight cardiac-related events in the amrubicin group, three were considered related to amrubicin and resolved without treatment discontinuation.

Conclusions: This was the first phase III study to compare amrubicin and docetaxel in patients with pretreated NSCLC. Amrubicin did not significantly improve the primary endpoint of PFS compared with docetaxel.

Clinical trial registration: NCT01207011 (ClinicalTrials.gov)

Key words: amrubicin, docetaxel, phase III study, non-small-cell lung cancer, chemotherapy
Introduction

Lung cancer is the most frequently diagnosed cancer and is the leading cause of cancer death worldwide [1]. Most cases of lung cancer are advanced, unreachable, and resistant to chemotherapy. About 85% of primary lung cancers are non-small-cell lung cancer (NSCLC), and chemotherapy with platinum-based anti-cancer regimens is often the only option for patients with Stage IIIIB and Stage IV cancers, especially those without EGFR mutations or ALK translocations. However, initial chemotherapy is frequently unsuccessful, necessitating secondary therapy.

Based on the results of randomized phase III studies of patients with NSCLC previously treated with platinum-based chemotherapy [2,3], docetaxel has been established as a standard regimen for second-line treatment for patients who have not already been given pemetrexed or erlotinib. However, pretreated NSCLC is a particularly difficult disease to treat and oncologists have a limited number of treatment options. In a prior phase III study in Western patients, docetaxel was associated with a longer time to progression (10.6 versus 6.7 weeks; P < 0.001) and median survival (7.0 versus 4.6 months; P = 0.047) than best supportive care [3]. In a study of Western patients treated with 75 or 100 mg/m² docetaxel, the median time to progression was 8.5 and 8.4 weeks, respectively, compared with 7.9 weeks in patients given vinorelbine or ifosfamide, while the median overall survival (OS) was 5.8, 6.6, and 5.4 months, respectively [2]. In a Japanese phase II study of low-dose (60 mg/m²) docetaxel [4], the overall response rate (ORR) was 18.2% (95% CI 5.1–40.3%) and the median survival time was 7.8 months, similar to the values observed in the Western phase III studies.

Amrubicin is a third generation anthracycline and a potent topoisomerase II inhibitor [5]. Several phase I/II and phase II studies have been conducted in which NSCLC patients were treated with amrubicin alone [6–8] or in combination with cisplatin [9]. In a phase II study of 37 patients with pretreated advanced NSCLC who received 35 mg/m² amrubicin on days 1–3 every 3 weeks, the ORR was 13.5%, median progression-free survival (PFS) time was 3.3 months, and the median survival time was 12.0 months [10]. Although grade 3 or 4 neutropenia occurred in 37.8% of patients, none had febrile neutropenia. However, because that study was uncontrolled, it is necessary to verify the efficacy of amrubicin in patients with previously treated NSCLC using an appropriate control group. Therefore, this study aimed to determine whether amrubicin was superior to docetaxel in terms of PFS, and to assess the safety and tolerability of amrubicin in Japanese patients with previously treated NSCLC. We used docetaxel (60 mg/m²) as the active comparator in this study because of its known efficacy in patients with previously treated NSCLC [2–4].

Methods

Study design

This was a multicenter, parallel-group, randomized, active-controlled, open-label study designed to evaluate the efficacy and safety of amrubicin in patients with previously treated NSCLC at 32 institutions. An open-label design was adopted because the two study drugs were distinguishable in terms of color and administration method. Further details regarding the study design are available in the Supplementary Materials, Online.

Patients

Patients aged ≥20 to <75 years with previously treated NSCLC diagnosed by histology/cytology were eligible if they had Stage IV (Tumor-Node-Metastasis) disease or Stage IIIIB unsuitable for radiotherapy, or had postoperative recurrence, providing they had a no response or disease progression after one or two prior chemotherapy regimens, which must include a platinum-based agent. We limited the upper age limit to 75 years because of the increased risk of serious toxicity in older patients [11]. All patients provided written informed consent after being provided with a study description. Patient allocation was managed by the registration center, which communicated by facsimile with the investigator.

Treatments

Amrubicin hydrochloride (Calsed®, Sumitomo Dainippon Pharma, Osaka, Japan) was intravenously administered at a dose of 35 mg/m²/day in ~20 ml of saline or 5% glucose over ~5 min. Amrubicin was administered on days 1, 2, and 3 of each 21-day cycle. Docetaxel was intravenously administered at a dose of 60 mg/m²/day (the approved dose in Japan), in physiological saline or 5% glucose over at least 1 h on day 1 of each course. Additional information regarding dose management and other treatments is presented in the Supporting Materials, Online.

Efficacy evaluations

The primary endpoint was PFS, which was measured from the date of enrollment to the confirmation of progressive disease (PD) or death from any cause. For surviving patients not classified as having PD, the data cut-off date was the last day of the imaging test. For patients who discontinued the study treatment but received post-study treatment before PD was confirmed, the data cut-off date was the last day of the imaging test before the post-study treatment. If PFS was not confirmed within 1 year after registration of the last subject, the data cut-off date was the day on which the last imaging test was performed within 1 year after registration of the last patient. OS was defined as the interval from enrollment to death from any cause. Surviving patients were censored at the final survival assessments.

Antitumor effects were assessed according to the Response Evaluation Criteria in Solid Tumours guidelines (version 1.1) [12] for a maximum of five lesions in total and a maximum of two lesions per organ. Outcomes included complete response (CR), partial response (PR), stable disease (SD), or PD, which were evaluated by the investigators at each site and by a central committee, and were used to calculate the tumor response (CR + PR) and disease control (CR + PR + SD) rates. Imaging was performed within 4 weeks before first administration, every 4 weeks for 24 weeks after starting course 1, and every 8 weeks until 1 year after the date of enrolling the last subject.

Safety assessments included laboratory tests (hematology and blood chemistry), urinalysis, vital signs, 12-lead electrocardiography, and monitoring of adverse events (AEs). AEs were graded according to Common Terminology Criteria for Adverse Events version 4.0. The measures taken to manage these events and their outcomes were reported.

Statistical analysis

The primary outcome was assessed in the full analysis set (all patients who satisfied the eligibility criteria and were administered the study drug at least once) and repeated in the per-protocol set (all subjects included in the full analysis set, except those with major protocol violations). Safety analyses were conducted in the safety analysis set, which included all patients who were administered the study drug at least once.

Baseline characteristics are presented as the mean ± standard deviation (SD) or N (%) of patients.

PFS and OS were compared between the two groups using log-rank tests stratified by histologic type and number of prior regimens, but not study site. Kaplan–Meier survival curves were plotted and the median PFS and OS were calculated with two-sided 95% Wald confidence intervals (CI). The hazard ratios were compared between groups using stratified Cox regression analysis,
with allocation factors (except study site) as stratification variables. Tumor response rates and disease control rates were compared between the two groups using Fisher's exact test. Subgroup analyses were conducted to identify possible prognostic factors for PFS, OS, or tumor responses.

In prior studies, the PFS for amrubcin and docetaxel were 3.3 and 2.0 months, respectively [6,13]. At a two-sided significance level of 5% and statistical power of 90%, 89 patients were required per group. To account for possible discontinuations or unevaluable data, we planned to enroll 100 patients per group.

**Results**

**Patients**

The first patient was enrolled in October 2010 and the last patient completed the study in July 2013. Of 101 patients randomized to each of the amrubcin and docetaxel groups, 66 and 54, respectively, completed the treatment (supplementary Figure S1, available at Annals of Oncology online). Both groups were well balanced in terms of their clinical characteristics (supplementary Table S1, available at Annals of Oncology online). The median number of amrubcin and docetaxel treatment cycles was 3 (range 1–36) and 3 (range 1–14), respectively. Fifteen patients in the amrubcin group and nine patients in the docetaxel group received ≥10 treatment cycles. The dose was reduced in 15 patients in the amrubcin group and 33 patients in the docetaxel group. The most common reason for a dose reduction in each group was grade 3 or worse neutropenia with fever in 6 and 11 patients in the amrubcin and docetaxel groups, respectively.

**PFS and OS**

The significance level of the final analysis was defined as \( \alpha = 0.04995 \), as predicted by the interim analysis. About 24 and 21 patients in the amrubcin and docetaxel groups, respectively, discontinued their allocated treatment and were censored in the analysis of PFS for the following reasons (amrubcin versus docetaxel): progressive disease (11 versus 7), could not start the subsequent treatment cycle (7 versus 2), deteriorating symptoms (2 versus 0), adverse event (0 versus 2), consent withdrawal (1 versus 7), and other reasons (3 versus 3). As shown in Figure 1A, the median PFS was similar in the amrubcin (3.6 months; 95% CI 2.1–3.8 months) and docetaxel groups (3.0 months; 95% CI 2.2–4.7 months), corresponding to a hazard ratio of 0.90 (95% CI: 0.65–1.25; \( P = 0.54 \)). The PFS was not significantly different between the amrubcin and docetaxel groups in subgroups of patients divided by histologic type, number of prior chemotherapy regimens, sex, age, or EGFR mutations (Figure 2A). Figure 1B shows the OS in both groups. The median OS in the amrubcin group (14.6 months; 95% CI 12.3–16.9 months) was similar to that in the docetaxel group (13.5 months; 95% CI 9.1–18.2 months), corresponding to a hazard ratio of 0.97 (95% CI 0.69–1.36; \( P = 0.86 \)). In a subgroup analysis, the OS was not significantly different between the two treatment groups (Figure 2B).

**ORR and disease control**

The ORR was 14.4% (14/97) in the amrubcin group and 19.6% (19/97) in the docetaxel group (\( P = 0.45 \)). The disease control rate was 55.7% in both groups (\( P = 1.00 \)) (Table 1). The ORR and disease control rate were comparable between the two treatment groups in subgroups analysed by patient and tumor characteristics (Table 1).

**Safety**

AEs occurred in all patients in both groups (supplementary Tables S2 and S3, available at Annals of Oncology online). The incidences of serious events, grade ≥3 events, and events leading to dose reduction, or treatment discontinuation were similar in both groups. Hematologic AEs were the most common AEs in both groups, and included neutropenia (98.0% versus 97.0%), leukopenia (98.0% versus 94.9%), and lymphopenia (67.4% versus 63.6%). Erythrnopenia (57.1% versus 32.3%) and thrombocytopenia (56.1% versus 19.2%) were more common in the amrubcin group, but most events were classified as grade 1 or 2. Grade ≥3 neutropenia occurred in 82.7% and 78.8% of patients in the amrubcin and docetaxel groups, respectively. Regarding non-hematologic AEs, nausea (52.0% versus 37.4%), anorexia (48.0% versus 51.5%), and alopecia (45.9% versus 61.6%) were common, but most events were classified as grade 1 or 2. Peripherad em and nail disorders were mostly seen in the docetaxel group, occurring in 17.2% and 10.1% of patients versus 1.0% and 0%, respectively, of patients in the amrubcin group. Interstitial lung disease occurred in 0% and 4.0% of patients in the amrubcin and docetaxel groups, respectively. There were three deaths (owing to interstitial lung disease, pulmonary embolism, and drowning in one patient each) in the docetaxel group, which were considered treatment-related. Drowning was classified as an adverse drug reaction and was probably related to neuropathy, for which a causal relationship with docetaxel could not be excluded. There was no treatment-related death in the amrubcin group.

Cardiotoxicity is an important concern regarding anthracyclines [14]. Eight cardiac-related events occurred in the amrubcin group (palpitations in two patients, ventricular extrasystole in two patients, and atrial fibrillation, atrial flutter, cardiac tamponade, and pericardial effusion in one patient each). Of these events, palpitations in both patients and ventricular extrasystole in one patient were considered related to amrubcin, but resolved while continuing treatment. The other events were considered unrelated to the study drug.

**Discussion**

The primary objective of this study was to confirm the superiority in PFS of amrubcin compared with docetaxel in patients with pre-treated NSCLC. Amrubcin at a dose of 35 mg/m² was associated with favorable PFS (median: 3.6 months), OS (median: 14.6 months), and ORR (14.4%). However, amrubcin was not statistically superior to docetaxel in this cohort of patients. The safety profiles of both drugs were fairly similar and tolerable. The most common AEs were erythrnopenia and thrombocytopenia in the amrubcin group, and edema and nail disorders in the docetaxel group. The incidence of dose reductions because of AEs was lower in the amrubcin group than in the docetaxel group.
An earlier phase II study showed that administration of amrubicin at a dose of 35 mg/m² achieved an ORR of 13.5% with median PFS and OS times of 3.3 and 12.0 months, respectively \[8\], which highlighted the clinical potential of amrubicin for patients with pretreated NSCLC. However, the absence of a control group meant the results needed verification in a subsequent phase III study.

The results of our study support those of the earlier phase II study in terms of PFS, OS and ORR. However, these values were not superior to those of docetaxel, which was used as an active comparator in our study. There may be some reasons for this finding, including the greater than anticipated PFS in the docetaxel group. For the present study, we estimated the sample size based on the median PFS (2.0 months) reported in an earlier study.

Figure 1 Kaplan–Meier plots of progression-free survival (A) and overall survival (B). FAS, full analysis set; HR, hazard ratio; CI, confidence interval.
phase III study of gefitinib and docetaxel in Japanese patients with previously treated NSCLC [13]. However, the PFS in the docetaxel group in our study was longer (3.0 months). It is of course possible that other factors explain the comparable findings in the two groups, including the higher number of patients who discontinued the study because they could not start the subsequent treatment cycle in the amrubicin group (11/98 [11.2%] versus 3/99 [3.0%]). Other clinically relevant findings include the

Figure 2 Forest plots of progression-free survival (A) and overall survival (B). AMR, amrubicin; CI, confidence interval; DOC, docetaxel; HR, hazard ratio.
extension of PFS to ≥10 cycles of treatment in 15.5% of amrubicin-treated patients compared with 9.3% of docetaxel-treated patients. Moreover, about half of the patients in the amrubicin group were treated with docetaxel after amrubicin, representing a potential treatment sequence in docetaxel-naïve patients.

Considering the AEs that occurred, the most notable were febrile neutropenia, which occurred in >10% of patients, and the slightly higher incidence of gastrointestinal toxicity, even though most of these AEs were classified as grade 1 or 2. It is worth noting that febrile neutropenia can be relieved by the prophylactic use of PEGylated granulocyte colony stimulating factor. Additionally, gastrointestinal symptoms can be reduced by the use of steroids or 5-HT3 receptor antagonists. Thus, if these AEs can be well managed, amrubicin may become a more desirable option for treatment of NSCLC.

Several factors that may limit the generalizability of the results warrant mention, including the enrollment of Japanese subjects and the use of a single dose of amrubicin (35 mg/m²/day), which may not be appropriate for other populations or ethnicities. Therefore, further studies may be necessary in other patient populations, especially non-inferiority studies in Western patients.

Recently, several studies [15,16] have demonstrated favorable results of nivolumab, human immunoglobulin G4 programmed death 1 immune checkpoint inhibitor antibody, in patients with pretreated NSCLC. The ORR for nivolumab was ~20% and the 1-year OS was 42%. Therefore, almost 80% patients did not experience tumor shrinkage for remission and cytotoxic agents are still necessary for the treatment of pretreated NSCLC.

In conclusion, although this study did not show superiority of amrubicin over docetaxel in terms of PFS, the results support those earlier Japanese studies in this setting [10,17].

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