attorney) and DNAR orders discussed and decided on by patients participating in a Phase I trial (4). However, it did not assess whether ACP should be started early in the incurable disease course because the patients involved had already received at least one chemotherapy regimen by the survey time. The CanCORS prospectively evaluated the incidence of EOL care discussions among patients with Stage IV lung or colorectal cancer, including where, when and with whom these discussions were taken (10). However, this prospective cohort study also did not determine whether to initiate ACP early in the incurable disease course because the baseline interview timing was ~4–6 months after diagnosis.

In this retrospective study, we investigated the implementation status of ACP in terms of two outcomes: the duration from the last day of chemotherapy to death and that from the day of a confirmed DNAR order to death. We found that the median C–D was 72 days for patients receiving intravenous chemotherapy. Greer et al. (11) reported that the median C–D for metastatic lung cancer patients receiving intravenous chemotherapy significantly differed between those who received early palliative care (64 days) and those who received standard care (40.5 days). D–D has been used as an outcome measure in several RCTs (12–14). These RCTs suggested that factors encouraging a DNAR decision, such as watching a video, email messages to oncologists, an information pamphlet and discussion, could lead to increasing the probability of a DNAR order and an early DNAR decision. Therefore, C–D and D–D are appropriate outcomes for evaluating the efficacy of early ACP.

Our study indicated that provision of prognosis information to patients was significantly associated with long C–D and D–D in multivariate analysis. Since there remains a lack of evidence supporting the belief that prognosis discussion causes depression, shortens life or diminishes hope, honest communication of a poor prognosis should be advocated (15). Several guidelines provide recommendations on how to disclose a poor prognosis, including two exceptional articles and a book by Back et al. (16–18). Transparency and reassurance about non-abandonment decreased participants' uncertainty and anxiety while increasing self-efficacy and satisfaction (19). In addition, reassurance about non-abandonment might provide realistic hopes that could be fulfilled (19). Our study reported that of 43 patients of prognosis informed to patients or patients and family members, such information was provided before and during first-line chemotherapy in 36 (84%) patients. However, the optimal timing to provide prognosis information to patients remains unclear. Future studies are needed to address this important issue.

In multivariate analysis, provision of information on supportive care before first-line chemotherapy was significantly associated with D–D. A previous prospective, longitudinal cohort study in the USA reported that EOL discussions were associated with less aggressive medical care near death and earlier hospice referrals (20). Another retrospective study in Japanese palliative care units reported that 68% of patients with decision-making capacity were involved in the DNAR decision. Temel et al. (21) suggested that early palliative care significantly improved patients' understanding of prognosis over time, which might impact decision-making regarding EOL care. Early provision of information on supportive care may therefore lead to better understanding of and appropriate EOL decisions, including a DNAR order.

This study has several limitations. First, it was a retrospective study with an inherent potential for bias. Second, only patients who died within a 3-year period at our institution were included. Thus, the median OS time of all patients was very short and there might be possibility of patients in this study seem to be not average patients with advanced lung cancer. Third, the implementation status of ACP provided by oral communication was inevitably missed because only electronic medical records and informed consent forms were evaluated. Finally, we did not evaluate patient-related factors, such as their understanding of informed consent, QOL and satisfaction. Therefore, future studies should be designed to evaluate these factors prospectively and the contents of information qualitatively.

Conclusion

Investigation of the ACP implementation status in NSCLC patients at our institution suggests that there is possible benefit from providing information on supportive care before first-line chemotherapy and informing patients about their prognosis in prolonging the duration of supportive care.

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Conflicts of interest statement

None declared.

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Phase II Study of Amrubicin Combined with Carboplatin for Thymic Carcinoma and Invasive Thymoma

North Japan Lung Cancer Group Study 0803

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Background: There has been no standard chemotherapy for advanced or recurrent thymic malignancies including thymic carcinoma (TC) and invasive thymoma (IT), though platinum and anthracycline have been reported as effective agents for the treatment of these diseases. The objective of this study was to evaluate the efficacy and safety of the combination of amrubicin (AMR), a new anthracycline agent, and carboplatin (CBDCA) in patients with advanced thymic malignancies.

Methods: Patients with histologically confirmed thymic malignancies received AMR (35 mg/m^2, days 1–3) and CBDCA (area under the curve 4.0, day 1) every 3 weeks. Patients who had received previous chemotherapy were treated with a reduced dose of AMR (30 mg/m^2). The primary end point was objective response rate (ORR), and secondary endpoints were progression-free survival, overall survival, and toxicity profile.

Results: From December 2008 to October 2012, 51 patients (33 TC and 18 IT) were enrolled. The median number of treatment cycles was four in each group. The ORR and progression-free survival were 30% (95% confidence interval, 14–46) and 7.6 months in the TC group, and 17% (95% confidence interval, 0–34) and 7.6 months in the IT group, respectively. The ORR of TC patients without previous chemotherapy (n = 19) was 42%. Although grade 3 or 4 hematological toxicities were common including neutropenia (82%) and febrile neutropenia (22%), these were transient and manageable. Nonhematological toxicities were moderate and no treatment-related death was observed.

Conclusions: The combination of AMR with CBDCA was active for TC with acceptable toxicity, although it was not effective for IT. Further investigation of this regimen for advanced TC is warranted.

Key Words: Thymic carcinoma, Invasive thymoma, Chemotherapy, Amrubicin, Phase II.

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Thymic carcinoma (TC) is a rare thymic epithelial tumor, which tends to metastasize and invade the surrounding tissues rapidly. Thus, the prognosis of TC is quite poor in the metastatic stage (2-year survival rate is approximately 50%).[1] Although invasive thymoma (IT) has a relatively good prognosis compared with TC, it is also a fatal disease when accompanied by distant metastasis. Patients with these advanced thymic malignancies are usually treated with systemic chemotherapy; however, due to the small number of patients with thymic malignancies compared with those with lung cancer, there has been no evidence available from large comparative studies and no standard treatment for these conditions. According to the guidelines of the National Comprehensive Cancer Network, patients with advanced TC should be treated with a regimen similar to that used for patients with IT.[2] Combined regimens consisting of platinum agent and anthracycline agents such as cisplatin, doxorubicin, and cyclophosphamide have been recommended for thymic malignancies,[3] although these do not show adequate efficacy and the severe toxicities (e.g., emesis or renal toxicity with cisplatin, and cardiac toxicity with anthracycline) sometimes produce a decline in the patient's quality of life.

Amrubicin (AMR) is a new anthracycline, which has achieved some promising results for advanced small-cell lung cancer in Japanese studies, as a single agent at a dose of 45mg/m^2 for three consecutive days, and also as a combined regimen with carboplatin (CBDCA, at a dose of area under

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the curve 4), at a dose of 35mg/m^2 on day 1 to 3.[4–6] Although care should be taken with regard to myelosuppression during the treatment with AMR, there have been few reports of cardiac toxicity induced by AMR to date. We postulated that the combination of AMR and CBDCA might show efficacy in treatment of advanced thymic malignancies with acceptable toxicities, and therefore conducted this phase II study.

PATIENTS AND METHODS

Patient Selection

This multicenter phase II trial was conducted in accordance with the Helsinki Declaration of the World Medical Association and the protocol was approved by the institutional review board of each participating institution. Patients older than 20 years with histologically confirmed TC or IT were enrolled in this study. Other eligibility criteria included Eastern Cooperative Oncology Group performance status 0 to 1, measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, estimated life expectancy greater than or equal to 3 months, and appropriate organ functions as follows: white blood cell count greater than or equal to 4000/mm^3, absolute neutrophil count greater than or equal to 2000/mm^3, platelets greater than or equal to 100,000/mm^3, hemoglobin greater than or equal to 9.0 g/dl, serum bilirubin less than or equal to 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase less than or equal to 100 IU/L, creatinine level less than or equal to 1.5 mg/dl, arterial oxygen pressure greater than or equal to 60 mmHg). Written informed consent was obtained from all the enrolled patients. Patients with symptomatic brain metastasis, interstitial lung disease, massive effusion requiring drainage, or severe comorbidities such as uncontrolled diabetes or cardiac disease were excluded. Patients who had received previous chemotherapy with doxorubicin within 400 mg/m^2 in total were included.

Treatment Schedule

AMR was diluted in 50ml of normal saline and administered by 10-minute intravenous infusion at a dose of 35 mg/m^2 on days 1 to 3 of each treatment cycle. Patients who had received previous chemotherapy were treated with a reduced dose of AMR (30 mg/m^2) to reduce the risk of myelotoxicity. CBDCA was diluted in 250 ml of 5% glucose solution or normal saline and administered by ≥30-minute intravenous infusion at a dose of area under the curve 4.0 on day 1 after AMR. Doses of both the agents were determined according to our previous phase II study of this combination for untreated small-cell lung cancer patients.[6] The treatment was repeated on a 21-day cycle. Premedication with corticosteroid and antiemetic serotonin antagonist was recommended. The dose of AMR was reduced by 5 mg/m^2 in each subsequent cycle in case of severe toxic effects such as grade 3 or more nonhematological toxicities, thrombocytopenia less than or equal to 20,000/mm^3, grade 4 neutropenia lasting greater than or equal to 4 days, or febrile neutropenia occurring in the previous cycle. Granulocyte colony-stimulating factor (G-CSF) was permitted for neutropenia but not for use as a prophylactic. No prophylactic antibiotic support was scheduled. All the patients were scheduled to receive at least three cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue the treatment. Subsequent chemotherapy after disease progression was permitted.

Patient Assessment

Patient assessment, including physical examination, complete blood count, and biochemistry, were repeated once a week in the first cycle and at least once per each cycle later. Measurement of tumors was carried out with respect to baseline assessment by computed tomography scans. Computed tomography examination was performed at least once per two cycles until disease progression. Tumor response was assessed according to RECIST version 1.1. Confirmation of complete and partial responses required at least 4 weeks duration of such responses, and stable disease required at least 4 weeks duration from the initiation of the protocol treatment. All response evaluations were performed by independent extramural review. Toxic effects were assessed according to the National Cancer Institute-Common Toxicity Criteria version 4.0.

Statistical Analysis

The primary end point of this study was objective response rate (ORR), and secondary endpoints included progression-free survival (PFS), overall survival, and toxicity profile. Overall survival was evaluated for a period from the introduction of protocol treatment to the date of death. Assuming that ORR of 45% and 75% would indicate potential usefulness whereas ORR of 20% and 50% would be at the lower limit of interest, with alpha = 0.10 and beta = 0.20, for TC and IT, respectively, the estimated accrual was 18 for each group. Survival estimation was performed using the Kaplan-Meier method. Differences between Kaplan-Meier curves were evaluated by log rank test.

RESULTS

Patient Characteristics

From December 2008 to October 2012, 51 patients (33 TC and 18 IT) were enrolled from 18 institutions in Japan. Because the patient accrual was relatively slow in the IT group, accrual of the TC group was also expanded accompanied with the IT group. Patient characteristics are shown in Table 1. Twelve patients had previously received platinum-based regimen such as CBDCA plus paclitaxel (nine patients) or cisplatin plus etoposide (four patients), and seven patients had been treated with doxorubicin mostly as doxorubicin, cisplatin, vincristine, and cyclophosphamide regimen before entering this study. Twenty-six (51%) patients received subsequent chemotherapy including CBDCA plus paclitaxel (12 patients) or S-1 (nine patients) after the protocol treatment.

Efficacy

The median number of treatment cycles was four in each group (range, 1–6 in TC, 2–15 in IT). Responses in all the 51 patients were evaluated. The ORR and disease control rates were 30% (95% confidence interval, 14–46) and 85% in

TABLE 1. Patient Characteristics

	Thymic Carcinoma (n = 33)	Invasive Thymoma (n = 18)
Gender		
Male/female	24/9	11/7
Age, median (range)	68 (39–78)	64 (44–76)
Performance status		
0/1	14/19	10/8
WHO classification		
A/B1/B2/B3	—	2/3/7/6
C	33	—
Prior chemotherapy		
Yes (1 regimen/2 regimens)	7/7	2/1
Regimen with doxorubicin	5	2
No	19	15
Prior surgery[a]		
Yes/no	10/23	9/9
Prior radiation[b]		
Yes/no	6/27	5/13

[a]Including preoperative radiation.
[b]Including postoperative radiation.
WHO, World Health Organization.

the TC group, and 17% (95% CI, 0–34), and 89% in the IT group, respectively (Table 2). The ORR of TC patients without previous chemotherapy (n = 19) was 42%.

At the data cutoff point in December 2013 when the median follow-up time of all the patients was 24 months, the median PFS and median survival time (MST) were 7.6 months and 27.3 months in the TC group and in the IT group were 7.6 months and 58.0 months, respectively (Fig. 1). The efficacy stratified by various clinical factors is listed in Table 3, and shows a significant difference in OS between those aged less than or equal to 65 and greater than 65 years (p = 0.0208).

Safety

Toxicities (greater than or equal to grade 2) are summarized in Table 4. Common toxicities greater than or equal to grade 3 were neutropenia (82%) including febrile neutropenia (22%), decreased hemoglobin (33%), and thrombocytopenia (20%). Twenty-eight (55%) patients required support with G-CSF for a median of 6 days (range, 2–11). Twelve (36%) patients in TC group and six (33%) patients in the IT group required dose reductions. Nonhematological toxicities were generally moderate. No cardiac toxicity was reported even in patients who had been previously treated with doxorubicin. No treatment-related deaths were observed.

DISCUSSIONS

The optimal chemotherapy for advanced thymic malignancies remains unclear although platinum- and anthracycline-containing triplet or quartet regimens such as cisplatin, doxorubicin, and cyclophosphamide or doxorubicin, cisplatin, vincristine, and cyclophosphamide have been used conventionally.[7,8] The efficacy of high-dose chemotherapy such as cisplatin, vincristine, doxorubicin, and etoposide has also been reported.[9] However, it is generally toxic and requires long-term G-CSF support due to the severe myelotoxicity, which seems to be unfavorable in general practice. Thus, an active regimen with acceptable toxicity for patients with advanced thymic malignancies is eagerly anticipated. Recently, a combination of CBDCA and paclitaxel was reported which achieved a moderate response. The ORRs of this regimen were 21.7% (90% CI, 9.0–40.4) for TC (n = 23) and 42.9% (90% CI, 24.5–62.8) for IT (n = 21), respectively, which is now recommended for TC in the National Comprehensive Cancer Network guidelines.[2,10] However, the associated severe peripheral neuropathy that reduces patient quality of life is a serious disadvantage of this regimen.[11]

This study revealed moderate efficacy of AMR and CBDCA in patients with advanced TC. In particular, the efficacy in TC patients without previous chemotherapy (ORR, 42%; 95% CI, 20–62) seems to be promising although it was from a subgroup analysis. The median PFS (7.6 months) and MST (27.3 months) in the TC group are also attractive compared with previous results with other regimens including CBDCA plus paclitaxel (PFS, 5.0 months; MST, 20.0 months) for advanced TC.[3,7,9,10,12,13] Thus, we believe further investigation of this regimen for TC patients is warranted. However, the efficacy of this regimen in IT patients is very disappointing. The reason for the low response rate in the IT group in this study remains unclear. It is possible that the evaluation by

TABLE 2. Response

	Thymic Carcinoma			Invasive Thymoma		
Prior Chemotherapy	**−**	**+**	**Total**	**−**	**+**	**Total**
n	**19**	**14**	**33**	**15**	**3**	**18**
Complete response	0	0	0	0	0	0
Partial response	8	2	10	2	1	3
Stable disease	8	10	18	11	2	13
Progressive disease	3	2	5	1	0	1
Not evaluable	0	0	0	1	0	1
Overall response rate (%) (95% CI)	42	14	30 (14–46)	13	33	17 (0–34)
Disease control rate (%) (95% CI)	84	86	85 (73–97)	87	100	89 (75–100)

CI, confidence interval.

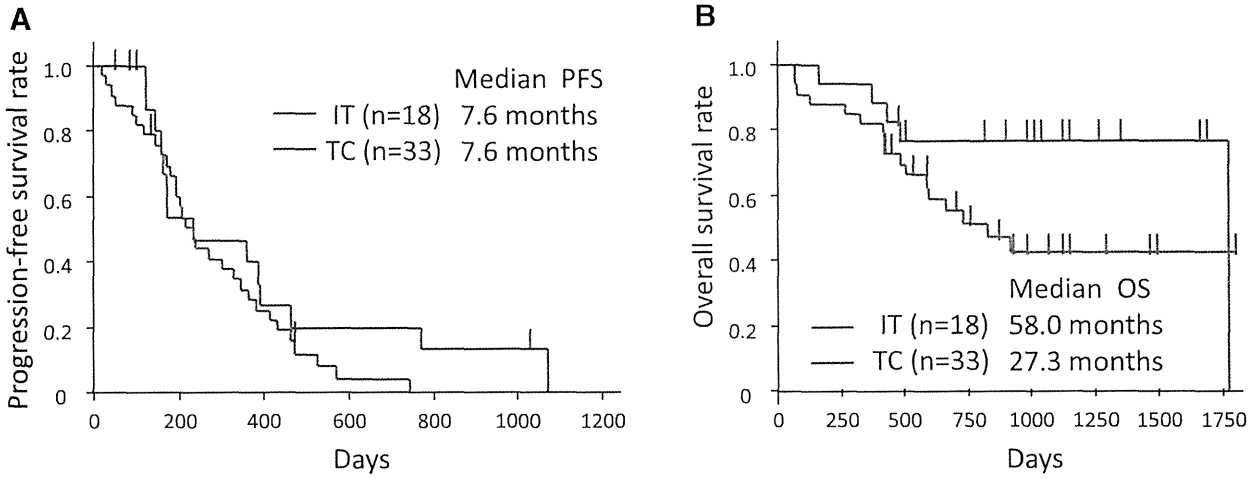

FIGURE 1. *A*, Kaplan–Meier curves for PFS and (*B*) OS of patients in TC group (blue line) and IT group (red line). Tick marks indicate patients for whom data were censored at the data cutoff point (December 2013). OS, overall survival; PFS, progression-free survival; TC, thymic carcinoma; IT, invasive thymoma.

TABLE 3. Efficacy Stratified by Various Clinical Factors

		n	ORR (%)	DCR (%)	MST (days)	1-Year OS (%)	MPFS (days)	1-Year PFS (%)
Age (years)[a]	≤65	25	8 (32%)	23 (92%)	1763	92	344	37
	>65	26	5 (19%)	21 (81%)	667	81	200	28
PS	0	24	7 (29%)	22 (92%)	NR	96	231	31
	1	27	6 (22%)	22 (81%)	1763	78	231	34
Gender	Male	35	11 (31%)	29 (83%)	NR	80	206	30
	Female	16	2 (13%)	15 (94%)	1763	100	231	38
Histology	A	2	0	2 (100%)	NR	100	771	100
	B1	3	0	2 (67%)	NR	67	168	NR
	B2	7	1 (14%)	7 (100%)	NR	100	171	43
	B3	6	2 (33%)	5 (83%)	1763	100	231	20
	C	33	10 (30%)	28 (85%)	831	82	231	28
Prior chemo	Yes	17	3 (18%)	15 (88%)	831	82	238	31
	No	34	10 (29%)	29 (85%)	NR	88	206	33
Prior DOX regimen	Yes	7	2 (29%)	6 (86%)	425	71	158	17
	No	44	11 (25%)	38 (86%)	1763	89	238	34
No. of prior chemo regimens	0	34	10 (29%)	29 (85%)	NR	88	206	33
	1	9	1 (11%)	7 (78%)	831	67	200	13
	2	8	2 (25%)	8 (100%)	1763	100	238	50
Prior surgery	Yes	19	6 (32%)	17 (89%)	1763	95	267	39
	No	32	7 (22%)	27 (84%)	831	81	213	28
Prior RT	Yes	11	3 (27%)	10 (91%)	831	91	200	27
	No	40	10(25%)	34 (85%)	1763	85	238	34

[a]A significant difference in OS between those aged ≤65 years and > 65 years ($p = 0.0208$, log rank test).
chemo. chemotherapy; DCR, disease control rate; DOX, doxorubicin; MPFS; median progression-free survival; MST; median survival time; NR, not reached; ORR, objective response rate; OS, overall survival; PS, performance status; RT, radiation.

RECIST might be unsuitable for some cases, depending on the shape of their tumor.[14] However, the PFS for IT patients in this study was also less than that of the previous studies for IT, so we conclude that this regimen is not active in IT. Because TC and IT are differently categorized, not only in terms of histology, but also with regard to clinical features and genetic backgrounds,[15] it is unsurprising that the efficacies of some agents differ in the two disease states.

Regarding the toxicity profile, the current combination of AMR and CBDCA is quite acceptable. Although the incidence of febrile neutropenia was relatively high, most events were observed during a short period and did not lead to severe

TABLE 4. Toxicity

	Number of Patients			
Grade (CTCAE)	**2**	**3**	**4**	**Grade 3/4**
Hematological				
Neutropenia	4	14	28	42 (82%)
Febrile neutropenia	—	9	2	11 (22%)
Anemia	15	16	1	17 (33%)
Thrombocytopenia	12	8	2	10 (20%)
Nonhematological				
Nausea	7	2	0	2 (4%)
Diarrhea	2	2	0	2 (4%)
Infection	2	2	0	2 (4%)
AST/ALT increased	1	1	0	1 (2%)
Bilirubin increased	2	0	0	0
Vomiting	1	0	0	0
Fever	1	0	0	0
Fatigue	1	0	0	0
Mucositis oral	1	0	0	0
Peripheral edema	1	0	0	0
Constipation	1	0	0	0
Hyperkalemia	1	0	0	0

ALT, alanine aminotransferase; AST, aspartate transaminase; CTCAE, common terminology criteria for adverse events.

infectious disease. Rather, the low incidence of severe nonhematological toxicities preserved the general condition of patients so that most received sufficient cycles of the treatment. Similar favorable toxicity profiles were observed in our previous studies,[5,6,16] which could add support to the use of this regimen.

This study has some limitations. First, the sample size was too small to draw the definite conclusions. However, it is difficult to conduct a large comparative study of thymic tumor due to its rare incidence, and to the best of our knowledge, this is the largest prospective study of chemotherapy for thymic malignancies. Second, the dosage of CBDCA may have been insufficient. Although we think that the current dosage was appropriate considering the current incidence of febrile neutropenia, there may be room to re-evaluate the balance of dosage of AMR and CBDCA.

In conclusion, although AMR combined with CBDCA was not effective in patients with IT, it was moderately active in TC with acceptable toxicities. Thus further investigation of this regimen for advanced TC is warranted.

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Overview

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

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

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

Methods

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

Results

Among 83 eligible patients (41 to CP, 42 to docetaxel), the objective response rates were 54% (95% confidence interval: 39%–69%) and 24% (95% confidence interval: 11%–37%) and median progression-free survival was 6.6 months and 3.5 months in the CP arm and the docetaxel arm, respectively. Severe neutropenia, febrile neutropenia, and nausea were

significantly frequent in the docetaxel arm, whereas toxicities in the CP arm were generally moderate. One treatment-related death was observed in the docetaxel arm.

Conclusion

The CP regimen achieved higher activity with less toxicity than single-agent docetaxel. Considering the results of this phase II trial and the IFCT-0501 trial, we have selected the CP regimen for a future phase III trial in elderly patients with advanced NSCLC.

Discussion

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

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

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

Trial Information

Disease:	Lung cancer – NSCLC
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	None
Type of study - 1:	Phase II
Type of study - 2:	Randomized
Primary Endpoint:	Objective Response Rate
Secondary Endpoint:	Progression Free Survival
Secondary Endpoint:	Overall Survival
Investigator's Analysis:	Active and should be pursued further

Drug Information

Drug 1:	
Generic/Working name:	Carboplatin
Drug class:	Platinum compound
Dose:	AUC 6.0 per
Route:	IV
Schedule of Administration:	day 1, every 4 weeks

Drug 2: **Generic/Working name:**	paclitaxel
Drug class:	Tubulin / Microtubules targeting agent
Dose:	70 mg (mg) per squared meter (m2)
Route:	IV
Schedule of Administration:	day1, 8, and 15, every 4 weeks
Drug 3: **Generic/Working name:**	docetaxel
Drug class:	Tubulin / Microtubules targeting agent
Dose:	60 mg (mg) per squared meter (m2)
Route:	IV
Schedule of Administration:	every 3 weeks

Patient Characteristics

Number of patients, male:	62
Number of patients, female:	21
Stage:	Stage III 16, IV 60, postoperative recurrence 7
Age:	Median (range): 76 (70-87)
Number of prior systemic therapies:	Median (range): 0
Performance Status:	ECOG 0 — 38 1 — 45 2 — 0 3 — 0 unknown — 0
Other:	Not Collected

Primary Assessment Method

Control Arm: Non-small cell lung cancer

Number of patients screened:	42
Number of patients enrolled:	42
Number of patients evaluable for toxicity:	42
Number of patients evaluated for efficacy:	42
Response assessment CR:	0%
Response assessment PR:	24%
Response assessment SD:	48%
Response assessment PD:	21%
Response assessment other:	7%
(Median) duration assessments PFS	3.5 months, CI: 2.5-4.6
(Median) duration assessments OS	11.8 months, CI: 6.5-17.1
Experimental Arm: Total Patient Population	
Evaluation method:	Other
Control Arm: Total Patient Population	
Evaluation method:	Other

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades
*No Change from Baseline/No Adverse Event							
Neutrophils/granulocytes (ANC/AGC)	0%	2%	22%	30%	44%	0%	100%

Regarding hematologic toxicity, the incidence of anemia and thrombocytopenia were slightly higher in the CP arm, although that of neutropenia and febrile neutropenia were significantly higher in the docetaxel arm. As to nonhematological toxicity, severe intestinal toxicity is more common in the docetaxel arm than the CP arm. Neurotoxicity in the CP arm was not severe. The total incidence of severe nonhematologic toxicities was higher in the docetaxel arm than the CP arm. One TRD due to neutropenia, pneumonia, and lethal arrhythmia was observed in the docetaxel arm.

Serious Adverse Events

Name	Grade	Attribution
neutropenia, pneumonia, and lethal arrhythmia	5	Probable

Assessment, Analysis, and Discussion

Completion: Study completed

Pharmacokinetics / Pharmacodynamics: Not Collected

Investigator's Assessment: Active and should be pursued further

Discussion

The objective response rate (ORR) of the current CP regimen was 54% (95% confidence interval: 39%–69%), which met the primary endpoint of this study. By comparison, the ORR of docetaxel was 24% (95% confidence interval: 11%–37%). In comparison with docetaxel, the CP regimen achieved longer PFS with less toxicity, excluding moderate anemia and thrombocytopenia. From these results, we have selected the CP regimen as a candidate in a future phase III trial for the elderly NSCLC population.

Although therapeutic recommendations are undergoing a re-evaluation, first-line chemotherapy for elderly patients with NSCLC has usually been monotherapy with agents such as vinorelbine or gemcitabine [1–6]. However, Quoix et al. recently reported the results of IFCT-0501, a phase III study comparing a similar CP regimen (with a carboplatin dose of area under the plasma curve of 6 mg/mL per minute on day 1 and paclitaxel at 90 mg/m^2 on days 1, 8, and 15 of each 4-week cycle) to monotherapy with vinorelbine or gemcitabine in elderly patients with a diagnosis of NSCLC. CP demonstrated a significant superiority in terms of efficacy (ORR and overall survival) [7]; however, severe toxicity in the CP arm, including a TRD rate of 4.4%, was of concern. Guided by our previous studies, we chose a paclitaxel dose of 70 mg/m^2 [8, 10], and this may be responsible for the lower toxicity observed with CP. TRDs were not observed in the CP arm in this study or in our previous study using the same regimen.

Regarding the efficacy of CP, the ORR and PFS in this study (54% and 6.6 months) are consistent with the results using the same regimen in our previous study (55% and 6.0 months) [8]. Because the evaluation of response in this study was performed by a centralized review blinded to the treatment, we believe the results were not biased. In fact, the ORR of docetaxel in this study (24%) was consistent with previous results using docetaxel in Japanese phase III trials for elderly NSCLC patients (23% in WJTOG9904 and 25% in JCOG0802) [6, 9]. Furthermore, despite patients in docetaxel arm receiving more subsequent chemotherapy, including a platinum doublet after their protocol treatment, the overall survival was still shorter than that of patients in the CP arm, suggesting that the most active regimen should be administered first. In addition, although the survival data of the CP arm in this study was much better than that achieved in IFCT-1501, a similar survival difference has also been observed in previous studies comparing Japanese patients with Western patients treated with the same chemotherapy regimen [11–13]. Because the efficacy of the carboplatin-based doublet was significantly superior to monotherapy in both IFCT-1501 and the current study, we believe elderly NSCLC patients with good performance status should be treated with proper doublet regimens as a standard of care.

Regarding toxicities due to paclitaxel, severe peripheral neuropathy is of the most concern. Ramalingam has reported the results in an elderly subgroup with advanced NSCLC from a previous phase III study that compared weekly paclitaxel (100 mg/m^2) with the standard 3-week paclitaxel (225 mg/m^2) schedule, both combined with carboplatin (area under the plasma curve: 6 mg/mL per minute). In this report, neurotoxicity of grade 3 or higher was lower in the weekly arm (9.5% in the standard arm vs. 5.5% in the weekly arm) [14]. Furthermore, nab-paclitaxel was recently approved for advanced NSCLC with a similar weekly schedule

that also showed a significantly lower rate of neurotoxicity compared with paclitaxel with the 3-week schedule, suggesting weekly administration may represent one approach to overcome the neurotoxicity related to paclitaxel. We chose a paclitaxel dose of 70 mg/m^2 based on our previous study because we had observed a favorable toxicity profile (greater than grade 3 neuropathy was 0%–3%) [8, 10]. We believe that the dose chosen for this study was appropriate for elderly NSCLC patients.

Other toxicities, including myelosuppression, grade 3 or higher neutropenia, neutropenic fever, and grade 3 or higher intestinal toxicities, were more common in the docetaxel arm, although rates of grade 3 or higher anemia and thrombocytopenia were slightly higher in the CP arm. Importantly, the rates of febrile neutropenia, an independent and poor prognostic factor in NSCLC patients receiving chemotherapy [16], has been consistently high (>10%) in the docetaxel arm in the current study and in previous Japanese studies. Given these observations and the fact that one TRD was observed in the docetaxel arm in this study, we infer that docetaxel might be more toxic than CP in elderly patients.

Our study has some limitations. First, because it is a phase II study, we cannot draw definite conclusions from this study alone. However, considering these results together with the positive results of a similar CP regimen in the recent IFCT-0501 trial, we believe that the CP regimen described is worthy of further investigation. Although the progression-free survival (PFS) of patients in the docetaxel arm in this study (3.5 months) may seem shorter than that of previous Japanese studies (5.5 months in WJTOG9904 and 4.4 months in JCOG0804), the median number of treatment cycles (i.e., four) was similar among these trials, suggesting that the difference may have occurred by chance or be related to some difference in the patient populations. We would note, however, that even if the PFS of docetaxel arm were 1 month longer than the current result, this would still appear inferior to the CP regimen that has demonstrated a PFS value in at least two trials of more than 6 months with a favorable risk-benefit ratio.

In conclusion, carboplatin plus weekly paclitaxel achieved higher activity with less toxicity in elderly patients with advanced NSCLC compared with monotherapy with docetaxel. Considering these results together with the results of the IFCT-0501 trial, we will select the CP regimen for use in a future phase III trial.

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Figures and Tables

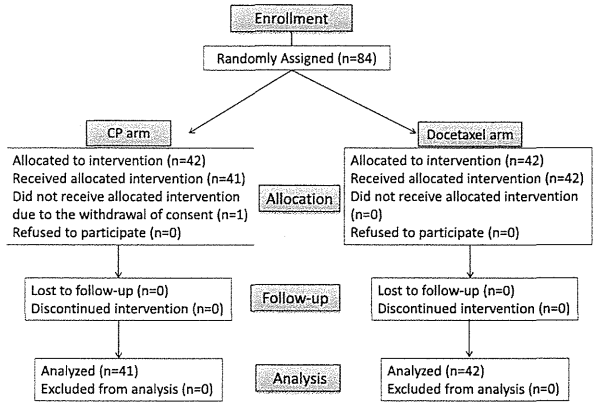


Figure 1. Enrollment.

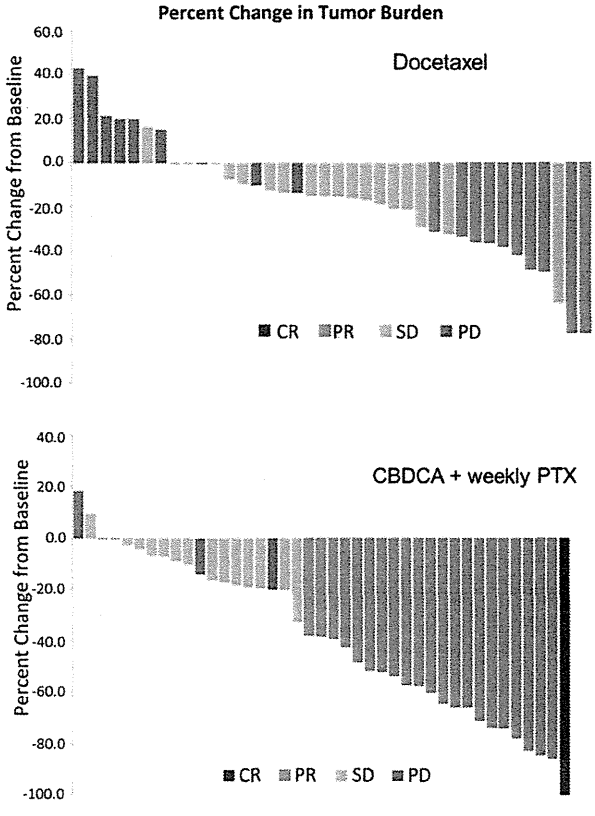


Figure 2. Waterfall plots of the docetaxel arm and the CP arm in this study.

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

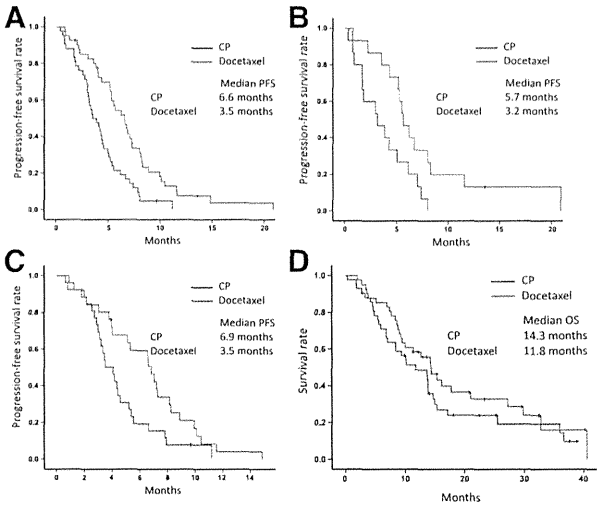


Figure 3. Survival rates. (A–C): Progression-free survival. (D): Overall survival.
Abbreviations: CP, carboplatin with weekly paclitaxel; OS, overall survival; PFS, progression-free survival.

Table 1. Patient characteristics

Characteristic	CP arm	Docetaxel arm
Gender, *n* (%)		
Male	35 (85)	27 (64)
Female	6 (15)	15 (36)
Age		
Median	76	77
Range	70–86	70–87
EGFR gene status, *n* (%)		
Wild	29 (71)	27 (64)
Mutant	2 (5)	2 (5)
Unknown	10 (24)	13 (31)
Performance status, *n* (%)		
0	19 (46)	19 (45)
1	22 (54)	23 (55)
Clinical stage, *n* (%)		
IIIA	0 (0)	1 (2)
IIIB	8 (20)	7 (17)
IV	29 (70)	31 (74)
Postoperative recurrence	4 (10)	3 (7)
Histology, *n* (%)		
Adenocarcinoma	23 (56)	23 (55)
Squamous cell	15 (37)	14 (33)
Large cell	0 (0)	1 (2)
Undifferentiated	3 (7)	4 (10)

Abbreviations: CP, carboplatin with weekly paclitaxel.

Table 2. Response

Result	CP arm	Docetaxel arm
Response, *n* (%)		
CR	1 (2)	0 (0)
PR	21 (51)	10 (24)
SD	14 (34)	20 (48)
Progressive disease	5 (12)	9 (21)
Not evaluable	0 (0)	3 (7)
Objective response rate (CR + PR) (95% confidence interval)	54% (39–69)	24% (11–37)
Disease control rate (CR + PR + SD)	88%	71%

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

Table 3. Hematological and nonhematological toxicity

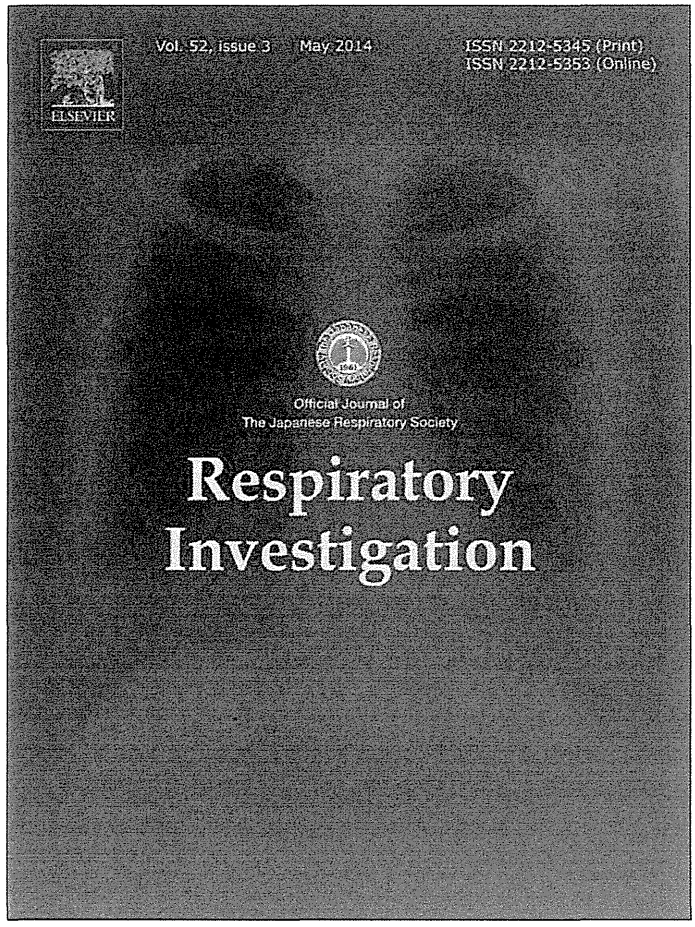
	CP arm (*n* = 41)						Docetaxel arm (*n* = 42)					
	CTCAE grade						CTCAE grade					
Toxicity	**1**	**2**	**3**	**4**	**5**	**Grade 3–4 (%)**	**1**	**2**	**3**	**4**	**5**	**Grade 3–4 (%)**
Hematological toxicity												
Anemia	9	24	4	2	0	14.6	26	9	2	1	0	7.1
Thrombocytopenia	11	8	2	2	0	9.8	4	0	0	0	0	0
Neutropenia	2	14	18	5	0	56.1	0	3	5	28	0	78.6
Febrile Neutropenia			1	0	0	2.4			10	0	1[a]	26.2
Nonhematological toxicity												
Nausea	12	6	1	0	0	2.4	15	3	6	0	0	14.3
Vomiting	2	2	0	0	0	0	5	0	0	0	0	0
Diarrhea	3	1	1	0	0	2.4	4	3	2	0	0	4.8
Peripheral neuropathy	7	5	1	0	0	2.4	2	0	0	0	0	0
Arthralgia, myalgia	5	0	0	0	0	0	2	0	0	0	0	0
Allergic reaction	2	1	0	0	0	0	5	0	0	0	0	0
Fatigue	2	2	0	0	0	0	5	2	0	1	0	2.4
Hypoalbuminemia	22	6	0	0	0	0	15	14	2	0	0	4.8
AST elevation	8	0	0	0	0	0	11	1	1	0	0	2.4
ALT elevation	7	1	1	0	0	2.4	10	3	0	0	0	0
Fever	3	1	0	0	0	0	3	0	0	0	0	0
Infection	2	3	2	0	0	4.8	3	0	1	0	0	2.4
Interstitial pneumonia	0	1	0	0	0	0	0	1	0	0	0	0
Ventricular tachycardia	0	0	0	0	0	0	0	0	0	0	1	2.4

[a]Treatment-related death.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CP, carboplatin with weekly paclitaxel; CTCAE, Common Terminology Criteria for Adverse Events.

Table 4. Postprotocol chemotherapy

Therapy	CP arm		Docetaxel arm	
Non-PD patients at data cutoff point	*n* = 3		*n* = 1	
PD patients after the protocol treatment	*n* = 38		*n* = 41	
	n	%	*n*	%
Combined regimen	4	10.5	14[a]	34.1
CBDCA + PTX	0	0	7	17.1
CBDCA + PEM	1	2.6	3	7.3
CBDCA + S-1	1	2.6	1	2.4
CBDCA + GEM	0	0	1	2.4
GEM + VNR	1	2.6	4	9.8
CPT + S-1	1	2.6	1	2.4
Monotherapy	16[a]	42.1	14[a]	34.1
Docetaxel	9	23.7	0	0
PEM	6	15.8	6	14.6
S-1	3	7.9	5	12.2
VNR	2	5.3	1	2.4
GEM	0	0	2	4.9
AMR	0	0	3	7.3
CPT	0	0	4	9.8
EGFR-TKI	2[a]	5.3	6	14.6
Gefitinib	2	5.3	3	7.3
Erlotinib	1	2.6	3	7.3
Any second-line chemotherapy	20	52.6	21	51.2
Any third-line chemotherapy	4	10.5	11	26.8
Any fourth-line or later chemotherapy	2	5.3	9	22.0

[a]Includes patient who received multiple regimens.
Abbreviations: AMR; amrubicin; CBDCA, carboplatin; CP, carboplatin with weekly paclitaxel; CPT; irinotecan; GEM, gemcitabine; PD, progressive disease; PEM, pemetrexed; PTX, paclitaxel; VNR, vinorelbine.



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Original article

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

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ABSTRACT

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

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

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

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

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1. Introduction

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

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

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

2. Patients and methods

2.1. Patient selection

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

2.2. Treatment schedule

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

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

2.3. Patient assessment

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

2.4. Statistical analysis

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

3. Results

3.1. Patient characteristics and treatment delivery

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

3.2. Efficacy

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

Table 1 – Patient characteristics.

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

Table 2 – Response.

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

CI, confidence interval.

3.3. Safety

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

4. Discussion

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