predictors and threshold values for acute radiation esophagitis in patients with stage III NSCLC who underwent concurrent chemoradiotherapy without ENI.

Materials and Methods

Patient Selection and Eligibility Criteria

The subjects of this study were patients with unresectable stage III NSCLC treated by high-dose 3-dimensional conformal radiotherapy (3DCRT) and concurrent chemotherapy as previously described in detail (14). Patients whose radiation therapy could not satisfy the eligibility criteria of normal tissue constraints at each allocated prescribed dose with 3DCRT planning were excluded from the study. The normal tissue constraints were lung V20 < 30%, maximal dose of the esophagus and brachial plexus <66 Gy, and spinal cord dose below 44 Gy in 22 fractions or 50 Gy in any fractions. The protocol was approved by the local institutional review board.

Treatment

Chemotherapy consisted of cisplatin (CDDP) of 80 mg/m^2 on day 1 and vinorelbine (VNR) of 20 mg/m^2 on days 1 and 8, repeated every 4 weeks for 3-4 cycles. External beam radiotherapy started on day 1 of the first cycle of chemotherapy, performed once daily at 2 Gy per fraction, 4-5 days a week, with 6-10 MV X-rays from linear accelerators (Clinac; Varian, Palo Alto, Calif. USA) using 5 mm width multileaf collimators (MLC). 3DCRT was planned using Xio® (CMS, St Louis, MO, USA) or Eclipse® (Varian, Palo Alto, Calif. USA). Gross tumor volume (GTV) for the primary tumor (GTVp) was determined through analysis for exhale and inhale phases in pulmonary windows of the chest CT, and FDG-PET was accepted to make distinction between GTVp and atelectasis. Nodal involvement was considered as present if the nodes were larger than 10 mm in the shortest diameter in CT images of mediastinal windows and/or if the nodes were FDG-positive. GTV of the nodal disease was defined as GTVn. Clinical target volume (CTV) was equivalent to GTVp and GTVn. ENI was strictly prohibited. Planning target volume (PTV) was defined as CTV plus 1.0 cm for the anterior, posterior, medial, and lateral margins and 1.0 to 2.0 cm for the superior and inferior margins as a setup margin and an internal motion by respiration. MLC margins were usually fixed at 0.5 cm.

3DCRT using multiple ports including oblique fields was acceptable but use of intensity-modulated radiotherapy (IMRT) was not allowed. Dose was prescribed to the isocenter in most patients and was calculated according to a superposition algorithm with a heterogeneity correction to cover the entire PTV with 90-110% of the prescribed dose. A 3DCRT replan according to tumor shrinkage or organ at risk (OAR) dose limits was not always necessary. The total dose fractionation was defined as 66 Gy in 33 fractions, 72 Gy in 36 fractions, and 78 Gy in 39 fractions as previously described (14).

DVH Analyses

All patients underwent radiotherapy planning CT (Aqullion LB®, Toshiba Medical Systems Corporation, Tokyo, Japan) within 1 week before the start of treatment, and the eligibility was finally confirmed by experienced radiation oncologists based on DVH parameters of OAR and normal tissue dose constraints mentioned above. For DVH analyses of the lungs, volumes of GTVp and GTVn were subtracted from bilateral lungs. The esophagus was delineated by its outer wall without considering cavity from the lower end of the cricoid cartilage to the upper end of the stomach. The maximum and mean irradiated doses and Vd of the esophagus were calculated by DVH analyses. Vd was defined as the percentage of the specified esophagus portion that was irradiated with more than d Gy. V5, V20, V35, V50, and V65 were calculated.

Toxicity Evaluation and Follow-Up

Patients who completed the protocol were followed up to monitor toxicity, though routine endoscopic examinations of the esophagus were not performed during and after the treatment. As acute morbidities, grade 2 or worse (G ≥2) radiation esophagitis, body weight loss G ≥2 during the treatment (more than 10% loss than baseline), grade 3 or worse (G ≥3) anemia (hemoglobin <8.0 g/dl), and hypoalbuminemia G ≥2 (serum albumin <3.0 g/dl) were evaluated until 10 weeks after treatment according to common terminology criteria for adverse events (CTCAE) version 4.0 (27). Any events of body weight loss G ≥2, anemia G ≥3, and hypoalbuminemia G ≥2 were defined as nutritional events.

Statistical Analysis

Patient and treatment characteristics were compared using the Mann-Whitney U test and Pearson's chi-square test. Overall survival (OS) was estimated from the start of treatment to the date of death considered as an event and censored at the time of the last follow-up. Time to progression (TTP) was estimated from the start of treatment to the date of progression considered as an event and censored at the time of the last follow-up. The cumulative rate of acute esophagitis was calculated from the start of treatment to the date of maximum grade of esophagitis. As for acute esophagitis, grade 2 or worse was considered as an event. OS, TTP, and acute esophagitis rate were calculated by the Kaplan-Meier method (28) and were compared by the log-rank test. Logistic regression analysis was performed with potential Vd that showed statistically significant differences between G ≥2 and G 0-1 radiation esophagitis in univariate analysis. Predictive ability was estimated by use of the area under the curve (AUC) of receiver operating characteristic (ROC) curves analysis which provides the sensitivity and specificity

associated with G ≥2 radiation esophagitis. The cut-off value was set to the median. A multivariable analysis testing for effects on G ≥2 radiation esophagitis of age (<70 vs. ≥70), albumin before treatment (≥3.5 vs. <3.5 mg/dl), stage (IIIA vs. IIIB), primary site (right vs. left lung), dose (<72 vs. ≥72 Gy), and the predictive Vd of the esophagus (≤ vs. > cut-off value) was performed using the Cox proportional hazards model. PASW 18.0 software for Windows (SPSS Japan, an IBM company, Chicago, IL, USA) was used for all statistical analyses. A p value of <0.05 was considered significant.

Results

Between August 2005 and February 2010, 32 patients were entered in this protocol. Patient, tumor, and treatment characteristics are shown in Table I and Table II. After a median follow-up period of 42.6 months (range: 7.9-69.6 months), 3-year OS and TTP rates were 64.3% and 31.3%, respectively. The maximal grades of acute radiation esophagitis occurring in 2-10 weeks after the start of treatment were classified into Grade 0-1, Grade 2, Grade 3, and Grade 4-5 in 11 (34.4%), 20 (62.5%), 1 (3.1%), and 0 (0%) of the patients, respectively (Figure 1). Between G ≥2 and G 0-1 radiation esophagitis, there was no significant difference in sex, age, stage, primary site, or pathology (Table I). In addition, volumes of GTV and PTV, prescribed dose, and number of chemotherapy cycles delivered had no impact on the incidence of acute esophagitis G ≥2 (Table II). Acute radiation esophagitis of G ≥2 did not have adverse impacts on nutritional events including body weight loss (G ≥2), anemia (G ≥3), and hypoalbuminemia (G ≥2).

As for radiation DVH variables, median irradiated dose of the esophagus was 1536 cGy (Table III). There were significant differences between the incidences of G ≥2 and G 0-1 acute radiation esophagitis in maximal and median doses, V5-V65 of the esophagus (Table III). In these statistically significant variables obtained from univariate analyses, only V35 of the esophagus remained significant by multivariate analysis as a predictor of G ≥2 radiation esophagitis (OR = 0.74 [95%CI; 0.60-0.91], p = 0.006) (Figure 1). V35 of the esophagus showed the highest AUC of 0.926 in the ROC curve. Cumulative rates of acute esophagitis according to V35 values of more than 20% vs. less are shown in Figure 2. While the incidence of acute esophagitis continued to increase until the end of radiation therapy in patients with V35 ≤ 20%, the incidence increased only until the 5th week and was statistically lower (88.9% vs. 35.7%, p = 0.027) in the patients with V35 < 20%. As compared with other factors concerning patient (age, albumin) and tumor (stage, primary site) and treatment (dose, esophagus V35) factors, V35 ≤ 20% of the esophagus

Table I

Patients and tumor characteristics with or without acute radiation esophagitis (Grade 2 or worse; CTCAE 4.0).

Characteristics		All	G ≥2 esophagitis	G 0-1 esophagitis	p
Age	Median (range)	61 (41-75)	59 (41-75)	61 (45-74)	Ns
Sex	Male	26	17 (80.9%)	9 (81.8%)	Ns
	Female	6	4 (19.0%)	2 (18.1%)	
T stage	1	12	6 (28.5%)	6 (54.5%)	Ns
	2	9	7 (33.3%)	2 (18.1%)	
	3	5	4 (19.0%)	1 (9.0%)	
	4	6	4 (19.0%)	2 (18.1%)	
N stage	0	1	1 (4.8%)	0 (0.0%)	Ns
	1	2	1 (4.8%)	1 (9.1%)	
	2	25	16 (76.1%)	9 (81.8%)	
	3	4	3 (14.3%)	1 (9.1%)	
Primary site	RUL	18	11 (52.3%)	7 (63.6%)	Ns
	RML	2	1 (4.7%)	1 (9.0%)	
	RLL	3	2 (9.5%)	1 (9.0%)	
	LUL	9	7 (33.3%)	2 (18.1%)	
	LLL	0	0 (0.0%)	0 (0.0%)	
Stage	IIIA	22	14 (66.7%)	8 (72.7%)	Ns
	IIIB	10	7 (33.3%)	3 (27.2%)	
Pathology	SCC	5	3 (14.2%)	2 (18.1%)	Ns
	Ad	25	16 (7.6%)	9 (81.8%)	
	Others	2	2 (9.5%)	0 (0.0%)	

Abbreviations: CTCAE = Common terminology criteria for adverse events; G = Grade; RUL = Right upper lobe; RML = Right middle lobe; RLL = Right lower lobe; LUL = Left upper lobe; LLL = Left lower lobe; SCC = Squamous cell carcinoma; Ad = Adenocarcinoma; Ns = Not significant.

Table II

Treatment and patient characteristics with or without acute radiation esophagitis (Grade 2 or worse; CTCAE 4.0).

Characteristics		All	G ≥2 esophagitis	G 0-1 esophagitis	*p*
GTV (ml)	Median (range)	77.3 (6.1-351.0)	83.4 (19.4-181.2)	38.7 (6.1-351.0)	0.14
PTV (ml)	Median (range)	306.5 (74.6-767.2)	323.0 (160.9-581.0)	214.3 (74.6-767.2)	0.11
	66 Gy/33 Fr	14 (43.7%)	8 (38.0%)	6 (54.5%)	
	72 Gy/36 Fr	12 (37.5%)	7 (33.3%)	5 (45.4%)	0.14
	78 Gy/39 Fr	6 (18.7%)	6 (28.5%)	0 (0.0%)	
Lung V20 (%)	Median (range)	24.9 (11.6-30.0)	26.4 (13.0-30.0)	22.2 (11.6-29.5)	0.08
CDDP (mg/m^2)	Median (range)	320 (80-320)	320 (80-320)	320 (80-320)	0.75
VNR (mg/m^2)	Median (range)	120 (40-160)	140 (40-160)	120 (40-160)	0.81
Body weight (kg)	Before	60.3 (46.3-86.0)	61.4 (47.9-76.1)	56.9 (46.3-86.0)	0.62
	After	58.3 (43.0-86.7)	59.3 (44.2-72.8)	55.0 (43.0-86.7)	0.72
	Loss (%)	−2.2 (−15.2-4.7)	−2.3 (−15.2-4.7)	−1.9 (−9.1-0.8)	0.90
Albumin (g/dl)	Before	3.8 (3.1-4.4)	3.8 (3.1-4.4)	4 (3.1-4.8)	0.40
	After	3.4 (2.4-3.9)	3.4 (2.7-3.8)	3.5 (2.4-3.9)	0.28
	Loss (%)	1.2 (−18.4-25.8)	0.0 (−18.4-25.8)	2.5 (−5.4-20.0)	0.35
Hemoglobin (g/dl)	Before	13.2 (10.1-16.3)	13.4 (10.1-16.3)	13 (11.3-14.6)	0.70
	After	8.9 (6.3-12.3)	8.4 (6.3-12.3)	9.1 (7.3-10.6)	0.14
	Loss (%)	−25.6 (−52.6-−8.3)	−27.3 (−52.6-−8.3)	−25.0 (−35.4-−14.9)	0.10
Nutrition event	Yes	9 (28.1%)	8 (38.1%)	1 (9.1%)	0.08
	No	23 (71.9%)	13 (61.9%)	10 (90.9%)	

Abbreviations: CTCAE = Common terminology criteria for adverse events; G = Grade, GTV = Gross tumor volume; PTV = Planning target volume; CDDP = Cisplatin; VNR = Vinorelbine.

was an only independent predictor (HR = 0.29 [95%CI; 0.09-0.85], $p = 0.025$) (Table IV).

Discussion

Since local failure has been reported to occur in one third to two-thirds of stage III NSCLC patients who have undergone chemoradiotherapy, the field set-up and dose must be further refined in thoracic radiotherapy (6.29-31). Acute radiation esophagitis is a common side effect in NSCLC patients undergoing concurrent chemoradiotherapy, and severe cases require hospitalization, nutritional intervention, and interruption of radiotherapy, which potentially aggravate local control (5-7). In some cases of severe acute esophagitis, the acute phase of reaction might continue to the late phase as a consequential toxicity (32). Thus, DVH predictors for acute radiation esophagitis have become important in the era of concurrent chemoradiotherapy with a dose escalation.

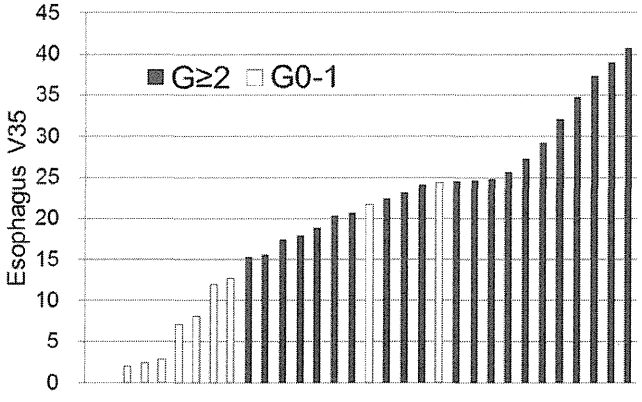

Figure 1: Bar chart showing V35 values of the esophagus. Stage III NSCLC patients are lined on the x-axis in ascending order of esophagus V35 values. White bars are for grade 0 or 1 (G 0-1) acute radiation esophagitis, and black bars are for grade 2 or worse (G ≥2) acute radiation esophagitis.

Previous studies on acute radiation esophagitis have revealed various DVH predictors (18-26). However, it is difficult to identify the best predictive DVH threshold for acute radiation esophagitis because those DVH values were reported with various endpoints (*e.g.*, G ≥1, G ≥2, or G ≥3). In the first place, the classification of RTOG grade 1 (mild dysphagia), grade 2 (moderate dysphagia), and grade 3 (severe dysphagia) esophagitis might be physician-dependent and ambiguous (7). Furthermore, there are differences in criteria between RTOG (33) and CTCAE (27). In CTCAE, grade 1 means any findings but asymptomatic, grade 2 is symptomatic and/or requiring medical treatment, and grade 3 is symptomatic and requiring nutritional intervention. Werner-Wasik *et al.* recommended that CTCAE be used for its simpleness and consistency (7). Accordingly, we employed CTCAE for toxicity classification in this study. By using RTOG criteria, Fernandes *et al.* reported that

Table III
DVH parameters and acute radiation esophagitis (Grade 2 or worse; CTCAE 4.0).

	Esophagitis G ≥2		Esophagitis G 0-1		UVA	MVA	ROC
	Median	Range	Median	Range	*p*	*p*	AUC
Max (cGy)	6764	5700-7839	6005	1520-6755	0.001	NA	0.874
Mean (cGy)	1613	1063-2635	995	154-1607	<0.001	NA	0.911
V5 (%)	41.7	21.9-54.1	34.1	3.7-71.4	0.045	0.828	0.719
V20 (%)	31.1	17.2-42.9	20.9	0.0-29.2	<0.001	0.681	0.896
V35 (%)	24.5	15.3-40.7	7.1	0.0-24.3	<0.001	0.006	0.926
V50 (%)	13.6	2.2-35.5	0.9	0.0-17.7	<0.001	0.974	0.903
V65 (%)	1.2	0.0-21.9	0	0.0-4.5	0.005	0.589	0.792

Abbreviations: CTCAE = Common terminology criteria for adverse events; G = Grade; UVA = Univariate analysis; MVA = Multivariate analysis; ROC = Receiver operating characteristic curves analysis; AUC = Area under the curve; NA = Not available.

G ≥3 acute radiation esophagitis is less frequently encountered in IFRT than in ENI (13). Our study also showed a very low incidence (3.1%) of G ≥3 acute radiation esophagitis, though CTCAE was used. IFRT without ENI is effective for avoiding acute radiation esophagitis even with an escalated dose and concurrent chemotherapy. Because of the low incidence of G ≥3 toxicity, G ≥2 acute esophagitis was considered as a surrogate event in this study. G ≥2 esophagitis in this study showed little impact on any nutritional event with a trend for a statistically significant difference (38.1% vs. 9.1%, $p = 0.08$).

Werner-Wasik *et al.* reported that volumes receiving >40-50 Gy correlated significantly with acute radiation esophagitis, but this might not apply to high-dose IFRT with concurrent chemotherapy (7). Our results demonstrated that V35 of the esophagus appears to be the most significant DVH predictor (OR = 0.74 [95%CI; 0.60-0.91], $p = 0.006$) in multivariate analysis. By dichotomizing at 20% of V35, (Figure 1) a significant difference was found in the cumulative incidence of acute radiation esophagits of G ≥2 at 10 weeks (38.4% vs. 89.4%, $p = 0.027$) (Figure 2) (Table IV). Twenty percent of V35 of the esophagus as a cut-off value for G ≥2 acute radiation esophagitis appears to be a stricter constraint than cut-off values recommended by other researchers (V20 <45%, Wei *et al.* (18); V35 <30%,

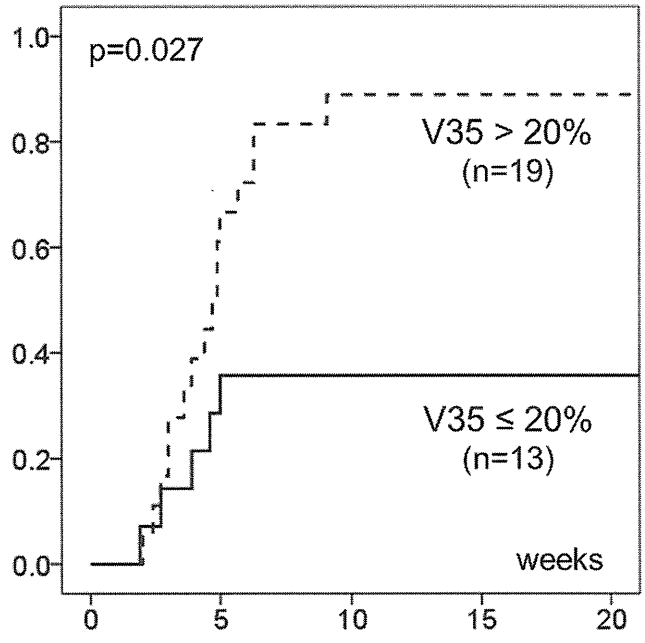

Figure 2: Cumulative rates of acute radiation esophagitis according to V35 of the esophagus. Solid line: V35 of the esophagus less than or equal to 20%, Broken line: V35 of the esophagus over 20%.

Table IV
Multivarite analysis of acute radiation esophagitis (Grade 2 or worse; CTCAE 4.0).

	Variate		Hazard ratio		*p*
Patient	Age	≥70	0.47	(0.13-1.69)	0.251
	Albumin	<3.5 mg/dl	1.18	(0.39-3.56)	0.762
Tumor	Stage	IIIA vs. IIIB	0.80	(0.28-2.26)	0.675
	Primary site	Right vs. Left	1.10	(0.41-2.92)	0.846
Treatment	Dose	≥72 Gy	0.90	(0.31-2.56)	0.843
	Esophagus V35	<20 %	0.29	(0.09-0.85)	0.025

Abbreviations: CTCAE = Common terminology criteria for adverse events; CDDP = Cisplatin; VNR = Vinorelbine.

Table V

Comparative table of treatment characteristics and predictive DVH values for acute radiation esophagitis in the literature.

		DVH values				Dose		Radiation esophagitis				Concurrent chemotherapy	
Authors	Published	Predictor	Constraint (%)	N	TRT	Median	Endpoint	Criteria	G ≥1 (%)	G ≥2 (%)	G ≥3 (%)	Regimen	Ratio (%)
Wei *et al.* (18)	2006	V20	<45	215	IFRT	63.5	G ≥3	RTOG	93	45	21	CBDCA+PTX	100
Takeda *et al.* (19)	2005	V35	<30	61	ENI	60	G ≥1	RTOG	59	11	0	Various	67
Belderbos *et al.* (20)	2005	V35	<31	156	ENI	66	G ≥2	RTOG	42	20	6	CDDP	24
Hirota *et al.* (21)	2001	V45	<45	26	ENI	60	G ≥2	CTCAE	100	69	8	CBDCA+PTX	100
Rodríguez *et al.* (22)	2009	V50	<30	100	IFRT	62	G ≥1	RTOG	59	29	4	Platinum doublet	100
Zhu *et al.* (23)	2010	V50	<11	157	IFRT	61	G ≥2	RTOG	NA	35	13	Various	41
Caglar *et al.* (24)	2010	V55	<50	109	ENI	60	G ≥3	CTCAE	87	52	24	Various	100
Singh *et al.* (25)	2003	D_{max}	<58 Gy	207	NA	70	G ≥3	RTOG	NA	NA	4	Various	26
Kim *et al.* (26)	2005	V60	<30	124	ENI	60	G ≥3	RTOG	NA	NA	12	Platinum doublet	60
This study	NA	V35	<20	32	IFRT	72	G ≥2	CTCAE	NA	62	3	CDDP+VNR	100

Abbreviations: DVH = Dose volume histogram; N = Number of cases; G = Grade; V_{dose} = Relative volume receiving specified dose or more; D_{max} = Maximal dose; TRT = Thoracic radiotherapy; IFRT = Involved field radiotherapy; ENI = Elective nodal irradiation; NA = Not available; RTOG = Radiation therapy oncology group; CTCAE = Common terminology criteria for adverse events; CBDCA = Carboplatin; PTX = Paclitaxel; CDDP = Cisplatin; VNR = Vinorelbine.

Takeda *et al.* (19); V35 <31%, Belderbos *et al.* (20); V45 <45%, Hirota *et al.* (21); V50 <30%, Rodríguez *et al.* (22); V50 <11%, Zhu *et al.* (23); V55 <50%, Caglar *et al.* (24); maximum dose <58 Gy, Singh *et al.* (25); V60 <30%, Kim *et al.* (26)) (Table V). In addition to differences in prescribed dose and chemotherapy, differences in the endpoint and criteria must be considered as causes of the differences described above. Another reason for the differences might be the stringent eligibility criteria in this study by which were enrolled only patients with lung V20 below 30% (median: 25.0, range: 11.6-30.0). And the small number of patients makes it difficult to test more number of independent parameters, consequently this is a major limitation of our study concerning a statistical and clinical applicability standpoint.

In conclusion, incidence of radiation esophagitis was low in our study and that radiation esophagitis is predictable by using a dose-volume histogram and can be reduced by minimizing the low-dose region of whole esophagus. Our proposal for limiting V35 of the esophagus to less than 20% might be important for minimizing radiation esophagitis in selected patients with stage III NSCLC undergoing high-dose IFRT with concurrent CDDP plus vinorelbine. Optimal DVH predictors for acute radiation esophagitis are probably different depending on the different clinical situation and therefore need to be studied further according to various combinations of radiation and chemotherapy.

Acknowledgments

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Brain metastases after definitive concurrent chemoradiotherapy in patients with stage III lung adenocarcinoma: Carcinoembryonic antigen as a potential predictive factor

Hidehito Horinouchi,[1,3] Ikuo Sekine,[1] Minako Sumi,[2] Yoshinori Ito,[2] Hiroshi Nokihara,[1] Noboru Yamamoto,[1] Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Division of Internal Medicine and Thoracic Oncology, [2]Division of Radiation Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

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The predictive factors for the development of brain metastases in patients with stage III non-small-cell lung cancer receiving concurrent chemoradiotherapy remain unclear. Several studies have suggested adenocarcinoma as a predictive factor of brain relapses. In the current analysis, we tried to identify the factors associated with brain metastases in stage III lung adenocarcinoma. The demographic and clinical characteristics, site and date of recurrence, and date of death were reviewed in patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemoradiotherapy. In total, 116 patients were identified with a median (range) age of 57 (35–74) years. Of these, 86 (74%) were men, all patients had platinum-based chemotherapy, and 100 (86%) received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy. Of the 95 patients with disease progression or recurrence, 19 (16%) developed brain metastases as the sole site of initial recurrence. A total of 43 (37%) patients developed brain metastases at some time during follow-up. Time to brain metastases was significantly associated with the pretreatment carcinoembryonic antigen (CEA) value, with a hazard ratio (95% confidence interval) of 2.64 (1.39–5.02, $P = 0.003$). Patients who developed brain metastases as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) than those with metastases other than brain. In conclusion, stage III lung adenocarcinoma patients with an elevated CEA value before treatment had a higher risk of developing brain metastases after chemoradiotherapy. Further effort is mandatory to control brain metastases in this patient population by a therapeutic strategy based on the tumor histology and pretreatment CEA value. (*Cancer Sci* 2012; 103: 756–759)

Recent advances in chemotherapy added to radiotherapy have dramatically improved the prognosis of patients with inoperable stage III non-small-cell lung cancer (NSCLC). The current standard treatment for these patients, concurrent thoracic radiotherapy and platinum-based chemotherapy, yields a 5-year survival rate of 16–23%, with acceptable acute and late toxicity.[1,2] However, many patients still die of recurrent disease. Brain metastases, as well as loco-regional recurrences, are the most frequent types of initial failure. Observational studies in patients with stage III NSCLC who underwent chemoradiotherapy with or without surgery showed that the first recurrent site was the brain in only 8–35% of patients, and brain and other sites in 4–10% of patients, resulting in brain metastases as the first recurrent site in 17–43% of patients.[1,3,4] Prophylactic cranial irradiation (PCI) has been tried to eradicate undetectable micrometastases before they become clinically apparent. Prospective randomized trials comparing PCI and observation in patients with locally advanced NSCLC treated by thoracic radiotherapy with or without chemotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, PCI is not indicated for all patients with stage III NSCLC treated with chemoradiotherapy, but it would improve prognosis if used to treat selected patients who are more likely to develop brain metastases. Several clinical factors have been identified to predict brain metastases in locally advanced NSCLC patients, but they are inconsistent among studies.[9–11] Of these clinical factors, adenocarcinoma histology was suggested to have a higher risk of brain relapses.[11–16] The objectives of this study were to identify factors associated with development of brain metastases in stage III adenocarcinoma patients who received concurrent chemoradiotherapy and to identify potential candidates for intervention to reduce brain relapses.

Materials and Methods

Patient selection. Patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital (Tokyo, Japan) between 1994 and 2005 were eligible for this study. Patients treated with sequential chemotherapy and thoracic radiotherapy were excluded because we have considered the standard care for the stage III NSCLC patients to be concurrent chemoradiotherapy, and therefore, the sequential treatment was given only to patients with poor general condition or to patients who had a tumor too large for radiotherapy initially but decreasing enough for radiotherapy after chemotherapy. All patients underwent a systematic pretreatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, CT scans of the chest and abdomen, a CT scan or MRI of the brain, a bone scintigram, and blood examinations including tumor markers.

Data collection and statistical analyses. Sex, age, performance status, body weight loss, carcinoembryonic antigen (CEA), clinical stage, nodal status, chemotherapy regimens, total dose of radiotherapy, tumor responses to treatment, sites and date of recurrence, and date of death were obtained from a retrospective medical chart review. As a routine clinical practice, tumor markers including CEA were examined in every patient eligible for chemotherapy and chemoradiotherapy before, during,

[3]To whom correspondence should be addressed.
E-mail: hhorinou@ncc.go.jp

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and just after the initiation of treatment. Receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to evaluate the cut points of CEA values to predict brain metastasis as the sole, or one of the first, relapse sites. Tumor histological classification was based on the criteria of the World Health Organization.[17] Patients were staged using the 6th edition of Union for International Cancer Control TNM classification for lung cancer.

Time to brain metastases was measured from the start of initial chemoradiotherapy to when the brain metastases were confirmed by a brain CT scan or MRI. Although we monitor brain metastases regularly as a routine follow-up imaging study after chemoradiotherapy, there might be diversity in the frequency and methods of monitoring. Patients who did not develop brain metastases at the last follow-up were censored at that time. Time to brain metastases was evaluated using the Kaplan–Meier method, the log–rank test, and Cox's proportional hazard model.

Sex, age, performance status, body weight loss, smoking status, CEA value, stage, T-factor, and nodal status were included as covariates in the multivariate analyses (Cox's proportional hazard model analyses). All of these analyses were carried out using STATA 11.1 software for Windows (StataCorp, College Station, TX, USA).

This study was approved by the president of the National Cancer Center Hospital. The institutional review board and ethics review committee decided to exempt this study from the usual review process because of its retrospective nature.

Results

In total, 116 patients were identified. Females accounted for 26% of the study group. The median age was 57 years. Almost all patients were in good general condition with a performance status of 0–1. Of the 116 patients, 63% had tumor factor (T-factor) 1–2 disease and 93% had nodal factor (N-factor) 2–3 disease. All patients received platinum-based chemotherapy, and 86% received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy (Table 1). The response rate was 82%, median survival time was 24.5 months, and the 5-year survival rate was 24% in this study group.

Disease progression or recurrence was noted in 95 (82%) patients. Brain metastases as the sole site of initial recurrence were noted in 19 (16%) patients, and both brain and other sites were involved in 17 (15%) patients (Table 2). Of the 19 patients who had isolated brain failure, 10 developed recurrences subsequently at additional sites other than the brain, three died of progressive brain metastases without progression in other sites, and two developed meningitis carcinomatosa. Another two patients also died, but the cause of death was not identified because they were lost to follow-up. Brain metastases were controlled by radiotherapy in the other two patients.

A total of 43 patients (37%) developed brain metastases at some time during the course of follow-up. We examined various cut points of CEA value and found 20 ng/mL gave a relatively better AUC (56.2%) by the ROC analysis. Time to brain metastasis was significantly associated with pretreatment CEA value. The responses of CEA during chemoradiotherapy and the CEA level just after chemoradiotherapy did not have significant correlation with brain relapses. The multivariate analysis using Cox's proportional hazard model showed that the hazard ratio (95% confidence interval [CI], *P*-value) of a CEA value $\geq$20 ng/mL was 2.64 (1.39–5.02, $P = 0.003$, Table 3) compared to a CEA value of < 20 ng/mL. Sex, age, performance status, body weight loss, smoking history, T-factor, nodal status, and stage were not associated with the time to brain metastasis (Table 3). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log–rank test, $P = 0.01$), respectively (Fig. 1).

Table 1. Characteristics of patients with stage III lung adenocarcinoma who participated in this study (*n* = 116)

Characteristic	*n*	%
Sex		
Female	30	26
Male	86	74
Age (years)		
Median (range)	57 (35–74)	NA
Performance status		
0	36	31
1	79	68
2	1	1
Body weight loss		
$\leq$4.9%	95	82
$\geq$5.0%	21	18
Smoking (pack-years)		
$\leq$10	29	25
$\geq$11	87	75
CEA (ng/mL)		
< 20	89	77
$\geq$20	27	23
Stage		
IIIA	57	49
IIIB	59	51
T-factor		
1–2	73	63
3–4	43	37
N-factor		
0–1	8	7
2–3	108	93
Chemotherapy type		
Cisplatin + vinorelbine	75	65
Cisplatin + vindesine + mitomycin	26	22
Nedaplatin + paclitaxel	8	7
Other combinations	7	6
Total radiation dose (Gy)		
60	100	86
<60	16	14

CEA, carcinoembryonic antigen; NA, not applicable; N-factor, nodal factor; T-factor, tumor factor.

Table 2. Sites of first recurrence in patients with stage III lung adenocarcinoma (*n* = 95)

Site of recurrence	*n*	%
Relapses including brain	36	38
Brain only	19	20
Brain and other sites	17	18
Sites other than brain	56	59
Unknown	3	3

Overall survival according to the first relapse site is shown in Figure 2. Patients who developed brain metastases only as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) compared to those with metastases other than brain.

Discussion

This study showed that CEA values before treatment were associated with time to brain metastasis in patients with stage III

Table 3. Time to brain metastases according to clinical factors in patients with stage III adenocarcinoma: Cox proportional hazard model analysis

Characteristic	Cox proportional hazard model (HR [95% CI])			
	Univariate	*P*-value	Multivariate	*P*-value
Sex				
Male	1	0.03	1	0.660
Female	2.00 (1.08–3.69)		1.24 (0.48–322)	
Age (years)				
≤57	1	0.17	1	0.110
≥58	0.65 (0.34–1.21)		0.58 (0.30–1.13)	
Performance status				
0	1	0.96	1	0.830
1–2	0.98 (0.53–1.83)		0.92 (0.44–1.92)	
Body weight loss (%)				
≤4.9	1	0.91	1	0.630
≥5.0	1.05 (0.47–2.36)		1.25 (0.51–3.05)	
Smoking (pack-years)				
≤10	1	0.01	1	0.290
≥11	0.43 (0.23–0.79)		0.58 (0.21–1.59)	
CEA				
<20	1	0.01	1	0.003
≥20	2.17 (1.17–3.99)		2.64 (1.39–5.02)	
T-factor				
1–2	1	0.39	1	0.880
3–4	0.75 (0.39–1.44)		0.84 (0.37–1.90)	
N-factor				
0–1	1	0.33	1	0.520
2–3	2.02 (0.49–8.38)		1.40 (0.50–3.88)	
Stage				
IIIA	1	0.93	1	0.770
IIIB	1.03 (0.57–1.87)		0.85 (0.30–2.46)	

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; N-factor, nodal factor; T-factor, tumor factor.

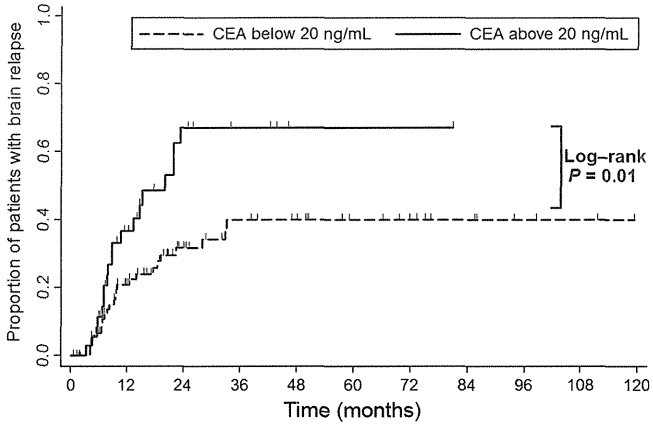

Fig. 1. Cumulative incidence of brain relapse in patients with stage III lung adenocarcinoma by carcinoembryonic antigen (CEA) value (ng/mL). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log-rank test, $P = 0.01$), respectively.

lung adenocarcinoma who received concurrent platinum-based chemotherapy and thoracic radiotherapy. This is the first report showing that the CEA value might be associated with a higher risk of brain metastases in locally advanced lung adenocarcinoma.

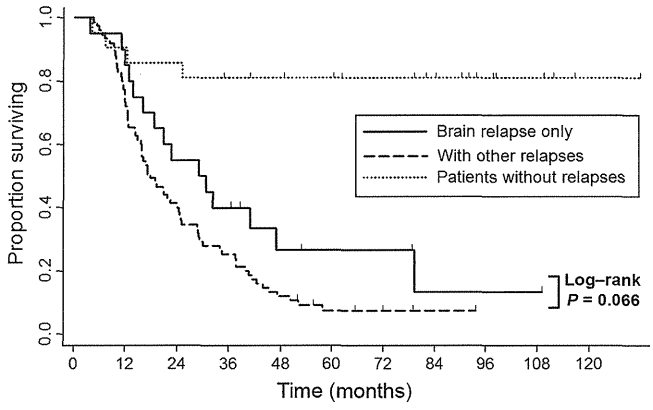

Fig. 2. Overall survival in patients with stage III lung adenocarcinoma according to the first relapse site. Dashed line, patients who developed extracranial recurrence with or without brain metastases; thick line, patients who developed brain relapse only; dotted line, patients who had no relapse. Patients who developed brain metastases as the first recurrent site had marginally better survival (log-rank test, $P = 0.066$) compared to those with metastases other than brain.

The median survival time (24.5 months) in the present study seemed better than the results observed in the study of Cox *et al.* (median survival time, 12.2–18.9 months) that included four clinical trials involving chemoradiotherapy.[12,18–21] The proportion of the participants whose first recurrent sites included brain metastases (38%, Table 2) in this study was substantially higher than the results observed in the analysis of Cox *et al.*[12] (16% with adenocarcinoma). Because the concurrent chemoradiotherapy with better survival failed to improve the proportion of brain relapses, the importance of the prevention of brain metastases has increased in this patient group. Furthermore, overall survival in patients who developed brain metastases as the sole site of the initial recurrence was marginally better than in those with metastases to other sites (log-rank, $P = 0.066$, Fig. 2) in our observation of patients with locally advanced lung adenocarcinoma. In fact, some patients with only brain relapses as the first recurrent site survived without further metastases after local treatment for the brain lesions.

Prospective randomized trials evaluating the effect of PCI in patients with locally advanced NSCLC after chemoradiotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, it is necessary to identify the clinical factors of patients who are more likely to develop brain metastases and would be good candidates for PCI. In retrospective analyses of patients with locally advanced NSCLC, adenocarcinoma histology was suggested to have a higher risk of brain relapses and be worthy of more attention concerning brain metastases.[11–16] Therefore, locally advanced lung adenocarcinoma was specifically analyzed to identify clinical factors predicting brain metastases.

Among patients with disseminated adenocarcinoma without indications for definitive thoracic radiotherapy, a high CEA value (over 40 ng/mL) before treatment might be associated with a higher risk of brain relapses.[22] The present study involving patients with locally advanced lung adenocarcinoma after chemoradiotherapy showed that the CEA value was significantly associated with the time to brain metastasis on multivariate analysis (Table 3). This result suggested that patients with stage III lung adenocarcinoma and elevated CEA values might be good candidates for interventions to prevent brain metastases.

This study had several limitations. First, the number of patients included in the analysis was relatively small because we selected patients with stage III lung adenocarcinoma who

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underwent concurrent chemoradiotherapy. Second, there might be diversity in the frequency and methods of monitoring brain metastases because of the retrospective nature of the analysis. Third, we could not determine significant factors to predict solitary brain relapses which might be cured by prophylactic brain intervention, mainly because the number of patients with solitary brain relapse was too small for efficient statistical analysis.

In conclusion, the present analysis implies that patients with elevated CEA values before treatment have a higher risk of developing brain metastases after chemoradiotherapy for locally advanced lung adenocarcinoma. Further effort is mandatory to evaluate the clinical relevance of CEA value to predict brain relapses and select candidates for prophylactic interventions in future prospective trials.

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Disclosure Statement

The authors have no conflicts of interest.

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Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin–paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002)

A. Inoue[1*], K. Kobayashi[2], M. Maemondo[3], S. Sugawara[4], S. Oizumi[5], H. Isobe[6], A. Gemma[7], M. Harada[8], H. Yoshizawa[9], I. Kinoshita[10], Y. Fujita[11], S. Okinaga[12], H. Hirano[13], K. Yoshimori[14], T. Harada[15], Y. Saijo[16], K. Hagiwara[17], S. Morita[18] & T. Nukiwa[1] for the North-East Japan Study Group

[1]Department of Respiratory Medicine, Tohoku University Hospital, Sendai; [2]Department of Respiratory Medicine, Saitama Medical University International Medical Center, Saitama; [3]Department of Respiratory Medicine, Miyagi Cancer Center, Miyagi; [4]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai; [5]First Department of Medicine, Hokkaido University School of Medicine, Sapporo; [6]Department of Medical Oncology, KKR Sapporo Medical Center, Sapporo; [7]Department of Internal Medicine, Division of Pulmonary Medicine, Infections Disease and Oncology, Nipppon Medical School, Tokyo; [8]Department of Respiratory Medicine, National Hospital Organization Hokkaido Cancer Center, Sapporo; [9]Bioscience Medical Research Center, Niigata University Medical & Dental Hospital, Niigata; [10]Department of Medical Oncology, Hokkaido University Graduate School of Medicine, Sapporo; [11]Department of Respiratory Medicine, National Hospital Organization Asahikawa Medical Center, Asahikawa; [12]Department of Respiratory Medicine, Kesennuma City Hospital, Miyagi; [13]Department of Respiratory Medicine, Iwate Prefectural Central Hospital, Morioka; [14]Division of Pulmonary Medicine, Anti-Tuberculosis Association Fukujuji Hospital, Tokyo; [15]Center for Respiratory Diseases, Hokkaido Social Insurance Hospital, Sapporo; [16]Department of Medical Oncology, Graduate School of Medicine, Hirosaki University, Hirosaki; [17]Department of Respiratory Medicine, Saitama Medical University, Saitama; [18]Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan

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Background: NEJ002 study, comparing gefitinib with carboplatin (CBDCA) and paclitaxel (PTX; Taxol) as the first-line treatment for advanced non-small cell lung cancer (NSCLC) harboring an epidermal growth factor receptor (EGFR) mutation, previously reported superiority of gefitinib over CBDCA/PTX on progression-free survival (PFS). Subsequent analysis was carried out mainly regarding overall survival (OS).

Materials and methods: For all 228 patients in NEJ002, survival data were updated in December, 2010. Detailed information regarding subsequent chemotherapy after the protocol treatment was also assessed retrospectively and the impact of some key drugs on OS was evaluated.

Results: The median survival time (MST) was 27.7 months for the gefitinib group, and was 26.6 months for the CBDCA/PTX group (HR, 0.887; $P = 0.483$). The OS of patients who received platinum throughout their treatment ($n = 186$) was not statistically different from that of patients who never received platinum ($n = 40$). The MST of patients treated with gefitinib, platinum, and pemetrexed (PEM) or docetaxel (DOC, Taxotere; $n = 76$) was around 3 years.

Conclusions: No significant difference in OS was observed between gefitinib and CBDCA/PTX in the NEJ002 study, probably due to a high crossover use of gefitinib in the CBDCA/PTX group. Considering the many benefits and the risk of missing an opportunity to use the most effective agent for EGFR-mutated NSCLC, the first-line gefitinib is strongly recommended.

Key words: EGFR mutation, gefitinib, individualized treatment, lung cancer

introduction

Two pivotal studies have revealed that somatic mutations in the kinase domain of the epidermal growth factor receptor (EGFR) strongly correlate with responsiveness to gefitinib, the first EGFR tyrosine kinase inhibitor (EGFR-TKI) used to treat non-small cell lung cancer (NSCLC) [1, 2]; subsequently, several phase II studies have demonstrated the promising efficacy of individualized treatment for advanced NSCLC patients with EGFR-TKI on the basis of EGFR gene mutation status [3–10]. Subsequently, we have conducted a phase III

*Correspondence to: Dr A. Inoue, Department of Respiratory Medicine, Tohoku University Hospital, 1-1, Seiryomachi, Aobaku, Sendai, 980-8574, Japan. Tel: +81-22-717-8539; Fax: +81-22-717-8549; E-mail: akinoue@idac.tohoku.ac.jp

study comparing gefitinib with the standard platinum doublet regimen, carboplatin (CBDCA, Nippon Kayaku, Tokyo) and paclitaxel (PTX, Bristol-Myers Squibb, Tokyo), as the first-line treatment for advanced NSCLC harboring EGFR gene mutations (NEJ002) [11]. The study revealed that gefitinib provided significantly longer progression-free survival (PFS), the primary endpoint of the study, than CBDCA/PTX. Other phase III studies also have demonstrated the superiority of EGFR-TKI over the platinum doublet regimen [12, 13]; thus EGFR-TKIs are now globally recognized as the standard first-line treatment for advanced NSCLC with sensitive EGFR mutations [14].

Regarding overall survival (OS), one of the secondary endpoints of NEJ002, the rate of events was <40% in the previous report, for which the data cutoff point was December 2009. Although our study was not powered for OS, we proceeded with this OS analysis to evaluate the long-term survival result for each treatment group. We updated the data for PFS, OS, and safety examined in a longer follow-up period and also assessed the impact of subsequent chemotherapy on OS in patients with EGFR-mutated NSCLC.

materials and methods

study design and treatment

Full details of the NEJ002 study have been published previously. Eligible patients had chemo-naïve advanced NSCLC with a sensitive EGFR mutation detected by the highly sensitive peptide nucleic acid-locked nucleic acid PCR clamp method [15]. Patients were randomly assigned (1:1) to gefitinib (250 mg/day) or CBDCA (AUC 6.0)/paclitaxel (Taxol, 200 mg/m^2) on day 1 every 3 weeks (up to six cycles). The primary endpoint of NEJ002 was to evaluate the superiority of gefitinib over CBDCA/PTX in PFS. The secondary endpoints included response rate, OS, quality of life (QOL), and safety profiles (see Supplementary data, available at *Annals of Oncology* online). Patients provided a written informed consent. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association. The protocol was approved by the institutional review board of each participating institution.

updated evaluation

PFS, OS, and safety data evaluated by the Common Terminology Criteria for Adverse Events version 3.0 were re-evaluated at the data cutoff point in December 2010 for the entire intent-to-treat population ($n = 228$), which was initially unplanned. Detailed information on subsequent chemotherapy carried out after the protocol treatment was also assessed for all patients retrospectively.

statistical analysis

The Kaplan–Meier survival curves were drawn for PFS and OS and compared using a two-sided non-stratified log-rank test with a significance level of 0.05. The hazard ratio (HR, gefitinib:CBDCA/PTX) and its two-sided 95% confidence interval (CI) were calculated by Cox regression analysis including only the treatment arm as a covariate. Subgroup analyses for OS, which were shown in a forest plot, were carried out to examine the interaction effect of treatment arm with age, gender, performance status, smoking status, type of histology, and type of EGFR mutation using a Cox regression model including treatment arm, each of the clinical factors, and their interaction effects as covariates. We did not account for adjustment for multiplicity due to the repetition of subgroup analyses, because we carried out them as exploratory analyses. Other comparative analyses were evaluated on the basis of a two-sided 5% significance level and 95% CI. All analyses were carried out using SAS for Windows release 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

updated PFS

Among the 224 patients assessable, the updated median PFS of the gefitinib group and that of the CBDCA/PTX group were 10.8 months and 5.4 months, respectively (HR, 0.322; 95% CI 0.236–0.438; $P < 0.001$), which was quite similar to the previous results (Table 1). The number of events for PFS at the last data cutoff (December 2010) was 98 in the gefitinib group and 101 in the CBDCA/PTX group. The rate of events for PFS slightly increased from the previous report (from 83% to 88%).

updated OS

At the last data cutoff point, the median follow-up time was 704 days (range 30–1659) and 69 death events were observed in each arm. The rate of events for OS increased from 36% in the previous report to 61% in the current study (Table 1). The MST and the 2-year survival rate were 27.7 months and 58%,

Table 1. Previous and updated results of survival

	Previous results (in 2009)		Updated results (in 2010)	
First-line treatment group	Gefitinib	CBDCA/PTX	Gefitinib	CBDCA/PTX
PFS				
Median PFS, months	10.8	5.4	10.8	5.4
Hazard ratio (95% CI)	0.296 (0.215–0.408)		0.322 (0.236–0.438)	
One-year PFS rate	42.1%	3.2%	43.8%	4.2%
Number of events (%)	87 (76%)	100 (91%)	98 (86%)	101 (92%)
Overall survival				
Median survival time, months	30.5	23.6	27.7	26.6
Hazard ratio (95% CI)	0.798 (0.517–1.232)		0.887 (0.634–1.241)	
1-year survival rate	84.7%	86.4%	85.0%	86.8%
2-year survival rate	61.4%	46.7%	57.9%	53.7%
Number of events (%)	39 (34%)	43 (38%)	69 (61%)	69 (61%)

CBDCA/PTX, carboplatin plus paclitaxel; CI, confidence interval; PFS, progression-free survival.

respectively, for the gefitinib group, and 26.6 months and 54% for the CBDCA/PTX group (HR, 0.887; 95% CI 0.634–1.241; $P = 0.483$) (Figure 1). No factor, including the type of EGFR mutation, had a substantial impact on OS between the groups (Figure 2).

safety

No additional serious adverse event (NCI-CTC grade ≥3) was reported in either group after the previous report. Briefly, the most common adverse events reported were rash and diarrhea with gefitinib, and appetite loss, sensory neuropathy, and myelotoxicities with CBDCA/PTX. The combined incidence of serious adverse events combined was significantly higher in the CBDCA/PTX group than in the gefitinib group (71.7% versus 41.2%; $P < 0.001$).

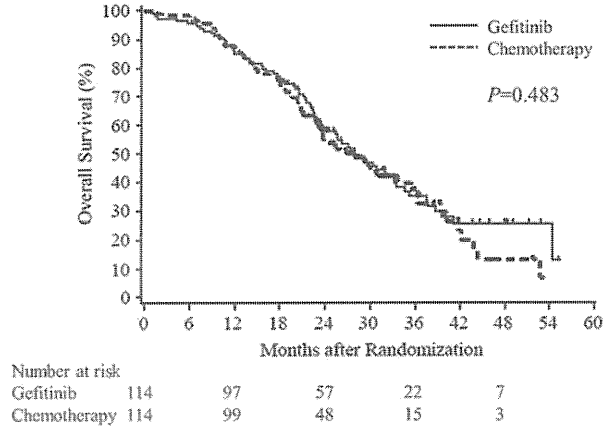

Figure 1. Kaplan–Meier curves for updated overall survival (OS) in the intent-to-treat population of NEJ002.

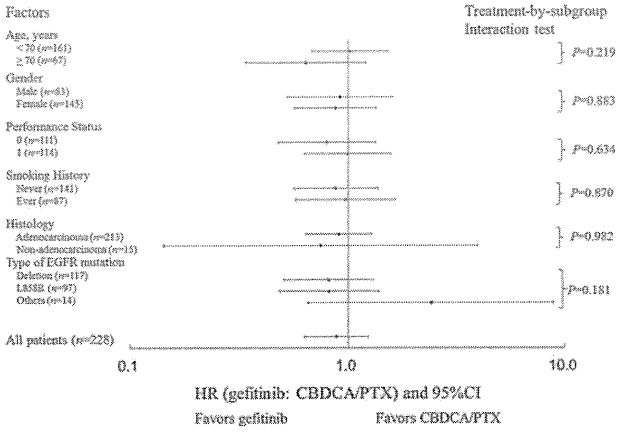

Figure 2. Forest plot of updated overall survival (OS) by clinical factors and the type of epidermal growth factor receptor (EGFR) mutation. Hazard ratio (HR) <1 implies a lower risk of death for patients treated with first-line gefitinb.

post-protocol chemotherapy

The chemotherapy regimens employed in NEJ002 are summarized in Table 2. Regarding the number of subsequent regimens, >50% of patients had received third-line chemotherapy or more, which was quite compatible with general practice in Japan (Figure 3A).

In the gefitinib group, 82 patients (72%) received at least one subsequent regimen. Among these, 74 patients (65%) were treated with the platinum doublet regimen including a crossover use of CBDCA/TXL in 59 patients (52%). Some patients received pemetrexed (PEM) combined with a platinum agent because it became available for the treatment of NSCLC in Japan in May 2009. Twelve patients went back on gefitinib and 32 received erlotinib in one of their later-line treatments. Among the 32 patients who received no subsequent regimen, 12 (11%) had been still treated with their first-line gefitinib at the data cutoff point (8 patients had still maintained their response to gefitinib, while 4 had continued gefitinib after the documentation of disease progression, in accordance with the patient's wishes). There were various reasons why the other 20 patients (18%) did not receive any subsequent regimens: deterioration of PS due to the progression of NSCLC ($n = 11$), interstitial lung disease due to gefitinib treatment ($n = 3$), exacerbation of co-morbidities ($n = 2$), or in accordance with the patient's wishes ($n = 4$). On the other hand, 113 patients (99%) in the CBDCA/PTX group had received at least one subsequent regimen, of whom 112 (98%) had moved to gefitinib.

The standard second-line chemotherapeutic agents PEM or docetaxel (DOC, Sanofi-Aventis K.K., Tokyo), which are used for advanced NSCLC, were used in 29% and 25% of patients in the gefitinib group, respectively, and in 16% and 19% of those in the CBDCA/PTX group, respectively. More than >20% of patients in both the arms received other agents such as irinotecan, S-1, gemcitabine, vinorelbine, or amrubicin as third- or later-line chemotherapy.

evaluation of the impact of key drugs on OS

To examine the impact of the platinum agent on OS of patients with EGFR-mutated NSCLC, we compared the OS of patients who received both gefitinib and a platinum agent in their treatment ($n = 186$) with that of patients who had never received a platinum agent ($n = 40$) in NEJ002. We found no significant difference between the OS of each group (Figure 3B). The number of patients who received a platinum agent but had not received gefitinib was only two in NEJ002.

We then assessed the impact of standard second-line agents (PEM and DOC) on OS. We divided patients who had received third-line or more in NEJ002 ($n = 131$) into two groups: the first group received EGFR-TKI, platinum agent, and PEM or DOC (P/D group, $n = 76$), and the second group received EGFR-TKI, platinum agent, but neither PEM nor DOC (no P/D group, $n = 55$). The MST of the P/D group was significantly longer than that of the no P/D group (34.8 months versus 22.6 months, $P = 0.003$) (Figure 3C).

Table 2. Summary of regimens for entire treatment in NEJ002

	Second-line *n* (%)	Third- or later-line *n* (%)	Total *n* (%)
First-line gefitinib group ($n = 114$)			
EGFR-TKI	8 (7.0)	34 (29.8)	114 (100)
Gefitinib	2 (1.8)	10 (8.8)	114 (100)
Erlotinib	6 (5.3)	26 (22.8)	32 (28.1)
Chemotherapy	74 (64.9)	52 (45.6)	76 (66.7)
Platinum based	71 (62.3)	11 (9.6)	74 (64.9)
CBDCA/PTX[a]	56 (49.2)	3 (2.6)	59 (51.8)
Platinum/PEM[b]	11 (9.6)	4 (3.5)	15 (13.2)
PEM (monotherapy)	2 (1.8)	16 (14.0)	18 (15.8)
DOC	0	28 (24.6)	28 (24.6)
Others[c]	1 (0.9)	26 (22.8)	27 (23.7)
First-line CBDCA/PTX group ($n = 114$)			
EGFR-TKI	109 (95.6)	42 (36.8)	112 (98.2)
Gefitinib	109 (95.6)	8 (7.0)	112 (98.2)
Erlotinib	0	33 (28.9)	33 (28.9)
BIBW2992	0	2 (1.8)	2 (1.8)
Chemotherapy	3 (2.7)	52 (45.6)	114 (100)
Platinum based	2 (1.8)	9 (7.9)	114 (100)
CBDCA/PTX	1 (0.9)	1 (0.9)	114 (100)
Platinum/PEM	0	4 (3.5)	4 (3.5)
PEM (monotherapy)	0	14 (12.3)	14 (12.3)
DOC	1 (0.9)	21 (18.4)	22 (19.3)
Others[c]	0	26 (22.8)	26 (22.8)

CBDCA/PTX, carboplatin plus paclitaxel; PEM, pemetrexed; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; DOC, docetaxel.
[a]Includes two CBDCA/PTX plus bevacizumab.
[b]Includes one CBDCA/PEM plus bevacizumab.
[c]Includes irinotecan, S-1, gemcitabine, vinorelbine, and amrubicine.

discussion

Although the NEJ002 study met its primary endpoint, in that gefitinib was superior to CBDCA/PTX in PFS, OS data were also important in evaluating the efficacy of the entire treatment including the regimens investigated. The current updated analysis demonstrated that the treatment course initiated with gefitinib achieved OS at least equivalent to a traditional treatment course initiated with a platinum doublet regimen for patients with advanced NSCLC harboring a sensitive EGFR mutation. Since the median follow-up time increased from 17 months in the previous report to 23 months in the current analysis, the OS results should become more accurate. We have already reported that the QOL was significantly better in the gefitinib group than in the CBDCA/PTX group in NEJ002 [16]. Moreover, gefitinib attained a high response rate, rapid improvement of symptoms, and exhibited low toxicity. Taking these factors together, we recommend the use of gefitinib as the first-line treatment.

There is a conservative opinion which states that the platinum doublet regimen should still be used as the first-line treatment for advanced NSCLC. This is because there has been no prospective study showing superiority of first-line EGFR-TKI over platinum doublet regimens for OS. Furthermore, some retrospective analyses have suggested that EGFR-TKI might be similarly effective in EGFR-mutated NSCLC regardless of the line at which it is used [17]. However, it is very important to recognize from our study that, though almost 100% of patients in the CBDCA/PTX group crossed over to gefitinib, the OS curve of the first-line gefitinib group was not inferior to that of the CBDCA/PTX group. While the risk associated with missing the administration of platinum agents after first-line gefitinib may be of concern, our *post-hoc* analysis suggested that the impact of the platinum agent on OS would not be larger than that of EGFR-TKI for patients with EGFR-mutated NSCLC. Figure 3B shows the MST of patients treated without platinum to be >2 years, which is a quite favorable result compared with previous historical data obtained when EGFR-TKI was not available. Thus, we feel that it is a concern if the chance to use gefitinib is missed when chemotherapy is carried out as the first-line treatment. The extremely high crossover rate in NEJ002 is hard to attain in general practice. In fact, only 51.5% of patients in the first-line CBDCA/PTX group received subsequent EGFR-TKI in the IPASS study [12]. Thus, we strongly recommend that the best drug should be used in the first instance.

Patients in the first-line gefitinib group tend to be treated with PEM or DOC monotherapy more intensively; this was because we supposed that some of these did not receive platinum doublet treatment for various reasons. However, we consider that the ideal treatment strategy for appropriate patients is to make use of available standard drugs. The most important finding in the *post-hoc* analysis shown in Figure 3C was that patients treated with EGFR-TKIs, platinum, and

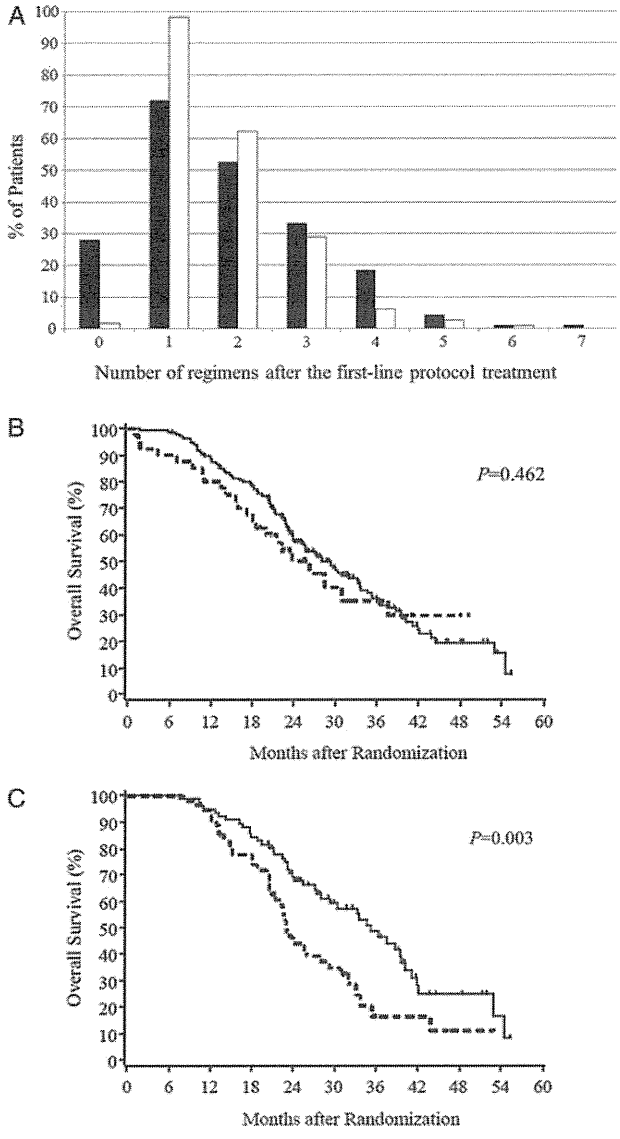

Figure 3. Evaluation of the impact of subsequent treatment on overall survival (OS) in NEJ002. The number of regimens that patients received after the first-line treatment with gefitinib (black bar) and that with chemotherapy (white bar) (A). The OS of patients treated with whichever line of gefitinib but not platinum (a dotted line) and those treated with both gefitinib and platinum (a solid line) (B). The OS of patients treated with gefitinib, platinum, with pemetrexed (PEM) and/or docetaxel (DOC; a solid line), and those treated with gefitinib, platinum but neither pemetrexed nor docetaxel (a dotted line) (C).

PEM/DOC achieved MST of around 3 years even though they had systemically advanced disease; however, the analysis may not conclusively show the difference between the two groups because they were not randomly assigned. This suggests that patients with EGFR-mutated NSCLC and with good PS enough to complete many lines of treatment may further benefit from a proper use of the above mentioned 'key drugs'. Although PEM and DOC were equally recognized as standard second-line agents at the time of the NEJ002 study [18], we now consider PEM to be more appropriate for EGFR-mutated NSCLC where adenocarcinoma is much common [14]. Since at least 14 patients (12%) failed to move to subsequent chemotherapy and ~20% of patients had never received platinum agents or PEM after their disease progressed in the gefitinib group, we think there may be a room for improvement of OS in these populations. Thus, we are now investigating a new treatment strategy, in which the first-line gefitinib is combined with CBDCA and PEM, for patients with EGFR-mutated NSCLC (UMIN000002789).

There are some limitations in the current analysis. First, the sample size of NEJ002 had inadequate power for evaluation of the difference in OS between the two groups. Since death events in one-third of patients have not yet occurred, the true OS curve may change slightly from that shown in this report. A meta-analysis combining several phase III studies and comparing EGFR-TKI with platinum doublet in an EGFR-mutated NSCLC population would be warranted. Second, the *post-hoc* analysis on subsequent chemotherapies may have been biased, because post-protocol treatments were not restricted under the NEJ002 protocol; however, they were very similar to those used in general practice in Japan. In addition, the unplanned comparative analysis between the subgroups shown in Figure 3B and C cannot draw definitive conclusions. It may be difficult to find whether the additive effect of platinum agents or PEM/DOC or good PS itself, that enabled patients to receive those agents irrespective of chemotherapy effects, influenced survival prolongation in the superior group more directly. However, we believe that they give us some interesting suggestions for future investigations such as that underway in our new study.

The reason there was no significant difference in OS between the first-line gefitinib group and the first-line CBDCA/PTX group in NEJ002 was very likely a high rate of crossover use of gefitinib in the CBDCA/PTX group. Considering the many benefits from EGFR-TKI use and the risk of missing an opportunity to use the most effective agent for treatment of EGFR-mutated NSCLC, the first-line gefitinib is strongly recommended in general practice for this population.

funding

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disclosure

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Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer

A. T. Shaw[1]*, A. M. Varghese[2], B. J. Solomon[3], D. B. Costa[4], S. Novello[5], M. Mino-Kenudson[6], M. M. Awad[1], J. A. Engelman[1], G. J. Riely[2], V. Monica[5], B. Y. Yeap[1] & G. V. Scagliotti[5]

[1]Department of Medicine Hematology/Oncology, Massachusetts General Hospital Cancer Center, Boston; [2]Department of Thoracic Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA; [3]Department of Medical Oncology, Peter MacCallum Cancer Centre, East Melbourne, Australia; [4]Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Boston, USA; [5]Department of Clinical and Biological Sciences, University of Torino, Torino, Italy; [6]Department of Pathology, Massachusetts General Hospital, Boston, USA

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Background: Anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC) is highly responsive to crizotinib. To determine whether ALK-positive NSCLC is also sensitive to pemetrexed, we retrospectively evaluated progression-free survival (PFS) of ALK-positive versus ALK-negative patients who had been treated with pemetrexed-based chemotherapy for advanced NSCLC.

Patients and methods: We identified 121 patients with advanced, ALK-positive NSCLC in the USA, Australia, and Italy. For comparison, we evaluated 266 patients with advanced, ALK-negative, epidermal growth factor receptor (EGFR)-wild-type NSCLC, including 79 with KRAS mutations and 187 with wild-type KRAS (WT/WT/WT). We determined PFS on different pemetrexed regimens.

*Correspondence to: Dr A. T. Shaw, Thoracic Oncology, Massachusetts General Hospital Cancer Center, Yawkey 7B-7508, 32 Fruit Street, Boston, MA 02114, USA. Tel: +1-617-724-4000; Fax: +1-617-726-0453; E-mail: ashaw1@partners.org

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A Phase II Study of Amrubicin as a Third-Line or Fourth-Line Chemotherapy for Patients With Non-Small Cell Lung Cancer: Hokkaido Lung Cancer Clinical Study Group Trial (HOT) 0901

TOSHIYUKI HARADA,[a] SATOSHI OIZUMI,[b] KENICHIRO ITO,[c] KEI TAKAMURA,[c] EIKI KIKUCHI,[b] TOMOYA KUDA,[d] SHUNICHI SUGAWARA,[d] AYA SUZUKI,[e] MAKOTO MAEMONDO,[e] YUKA FUJITA,[f] ICHIRO KINOSHITA,[g] AKIRA INOUE,[h] FUMIHIRO HOMMURA,[i] YUTAKA KATSUURA,[j] HIROTOSHI DOSAKA-AKITA,[g] HIROSHI ISOBE,[k] MASAHARU NISHIMURA,[b] HOKKAIDO LUNG CANCER CLINICAL STUDY GROUP

[a]Hokkaido Social Insurance Hospital, Sapporo, Japan; [b]Hokkaido University School of Medicine, Sapporo, Japan; [c]Obihiro Kousei Hospital, Obihiro, Japan; [d]Sendai Kousei Hospital, Sendai, Japan; [e]Miyagi Cancer Center, Natori, Japan; [f]Asahikawa Medical Center, Asahikawa, Japan; [g]Hokkaido University Graduate School of Medicine, Sapporo, Japan; [h]Tohoku University Hospital, Sendai, Japan; [i]Sapporo City General Hospital, Sapporo, Japan; [j]Saiseikai Fukushima General Hospital, Fukushima, Japan; [k]Kokka-komuin Kyosai-kumiai Rengokai Sapporo Medical Center, Sapporo, Japan

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Amrubicin • Chemotherapy • Fourth line • Non-small cell lung cancer • Third line

ABSTRACT

Amrubicin, a third-generation synthetic anthracycline agent, has favorable clinical activity and acceptable toxicity for the treatment of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer. We conducted this study to evaluate the efficacy and safety of amrubicin for advanced NSCLC patients as a third- or fourth-line therapy. Eligible patients had recurrent or refractory advanced NSCLC after second- or third-line therapy. Patients received amrubicin, 35 mg/m^2 i.v. on days 1–3 every 3 weeks. The primary endpoint was the disease control rate (DCR). Secondary endpoints were the overall survival (OS) time, progression-free survival (PFS) time, response rate, and toxicity profile. Of the 41 patients enrolled, 26 received amrubicin as a third-line and 15 received it as a fourth-line therapy. The median number of treatment cycles was two (range, 1–9). Objective responses were complete response (n = 0), partial response (n = 4), stable disease (n = 21), progressive disease (n = 15), and not evaluable (n = 1), resulting in a DCR of 61.0% (95% confidence interval, 46.0%–75.9%). The overall response rate was 9.8% (95% confidence interval, 0.6%–18.8%). The median PFS interval was 3.0 months, median OS time was 12.6 months, and 1-year survival rate was 53.7%. Grade 3 or 4 hematological toxicities were neutropenia (68%), anemia (12%), thrombocytopenia (12%), and febrile neutropenia (17%). Nonhematological toxicities were mild and reversible. No treatment-related deaths were observed. Amrubicin showed significant clinical activity with manageable toxicities as a third- or fourth-line therapy for patients with advanced NSCLC. This study provides relevant data for routine practice and future prospective trials evaluating third- or fourth-line treatment strategies for patients with advanced NSCLC. *The Oncologist* 2013;18:439–445

Implications for Practice: There is a paucity of prospective studies that specifically address the role of cytotoxic agents as a third-line therapy for non-small cell lung cancer (NSCLC) patients. Amrubicin showed significant clinical activity with manageable toxicities as a third- or fourth-line therapy for advanced NSCLC. Amrubicin could be a better candidate in these settings for routine practice.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide [1]. First-line therapies, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with *EGFR* mutations, as well as platinum-based chemotherapy in conjunction with third-generation antitumor agents significantly improve survival outcomes and quality of life in patients with advanced non-small cell lung cancer (NSCLC) [2–5]. Despite these favorable outcomes, most patients receiving first-line therapy experience disease progression and require salvage therapy. Second-line therapy also has beneficial effects on survival and quality of life outcomes [2, 6, 7].

Docetaxel, pemetrexed, gefitinib, and erlotinib are considered standard second-line therapies based on several randomized controlled trials [6–9]. Because of the improved efficacy of first-line, second-line, and maintenance therapy

Correspondence: Toshiyuki Harada, Ph.D., Center for Respiratory Diseases, Hokkaido Social Insurance Hospital, 3–18, 1–8, Nakanoshima, Toyohira-ku, Sapporo 062-8618, Japan. Telephone: 81-11-831-5151; Fax: 81-11-821-3851; E-mail: t-harada@hok-shaho-hsp.jp Received July 19, 2012; accepted for publication November 8, 2012; first published online in *The Oncologist Express* on February 26, 2013. ©AlphaMed Press 1083-7159/2013/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2012-0308

for NSCLC, a high proportion of patients (26%–38%) receive third-line therapy [10, 11]. Thus, there is an urgent need for new third-line therapy options. To date, there is a paucity of studies that address the role of third-line therapy, and they are primarily retrospective analyses [12–14].

Amrubicin, a completely synthetic 9-amino-anthracycline, is a potent inhibitor of DNA topoisomerase II [15]. A phase II study of amrubicin in both NSCLC and SCLC patients demonstrated promising results and tolerable toxicity [16, 17]. The clinical significance of amrubicin has recently focused on the treatment of recurring lung cancer. A phase I and a pharmacokinetic study of amrubicin in previously treated NSCLC and SCLC patients recommend an amrubicin dose of 35 mg/m^2 per day on three consecutive days every 3 weeks [18]. Amrubicin is a promising third-line therapy agent because it has a different mechanism of action from those of other available anticancer agents.

Currently, there is no prospective study that specifically addresses the role of third-line therapy for NSCLC patients. We therefore conducted a multicenter prospective phase II trial of amrubicin (35 mg/m^2) to confirm the efficacy and safety of the drug in NSCLC patients as a third- or fourth-line therapy.

Patients and Methods

Patient Eligibility

Eligible patients met the following criteria: histologic or cytologic confirmation of NSCLC, recurrent or refractory disease after two or three previous treatment regimens, measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2, age ≤75 years, adequate bone marrow function (leukocyte count ≥3,000/mm^3, neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, and hemoglobin content ≥9.0 g/dL), adequate function of other organs (total bilirubin concentration ≤1.5 mg/dL, aspartate transaminase and alanine transaminase levels ≤2.0× the upper limit of normal, and creatinine clearance ≥50 mL/minute), P_aO_2 ≥60 Torr or S_pO_2 ≥95%, left ventricular ejection fraction ≥60% on echocardiography, and a life expectancy ≥3 months.

Patients with previous amrubicin therapy, exceeding the critical dosage in prior anthracycline drug therapy, using corticosteroid or immunosuppressive drugs, with an active infectious disease with serious medical complications (active peptic ulcer, heart disease, diabetes mellitus, or cerebrovascular disease), with radiographic signs of interstitial pneumonia or pulmonary fibrosis, with third-space fluid collection requiring drainage, who were lactating or pregnant, with symptomatic brain metastasis, or with active concomitant malignancy were deemed ineligible.

This study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines [19]. The protocol was approved by the institutional review boards of all participating institutions, and all patients provided written informed consent before treatment.

Treatment Plan

Amrubicin was dissolved in 20 mL physiological saline and was administered i.v. for >5 minutes at a dose of 35 mg/m^2·per day on days 1–3 every 3 weeks. All patients received at least two cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue treatment.

Subsequent cycles of treatment were withheld until the following criteria were satisfied: the leukocyte count was ≥3,000/mm^3, the neutrophil count was ≥1,500/mm^3, the platelet count was ≥100,000/mm^3, total bilirubin was ≤2.0 mg/dL, there was no infection, the ECOG PS score was ≤2, and the grade of any nonhematologic toxicity was ≤2. If these criteria were not satisfied within 36 days after the onset of the last treatment, the patient was removed from the study. The dose of amrubicin was reduced to 30 mg/m^2 per day for cases of leukopenia or neutropenia of grade 4 persisting for >4 days, thrombocytopenia of grade 4 or requiring platelet transfusion, febrile neutropenia, or nonhematologic toxicity of grade ≥3 (except for anorexia, nausea, or alopecia) during the previous course. If these toxicities occurred after reduction of the amrubicin dose to 30 mg/m^2 per day, the dose was further reduced to 25 mg/m^2 per day. A third reduction was not permitted, and the protocol treatment was terminated. Use of prophylactic antibiotics was not permitted.

Evaluation

Baseline assessment included a physical examination; CBC with differential, hepatic, and renal function tests; urinalysis; 12-lead electrocardiogram; echocardiogram; and chest radiography. Visible and palpable tumors were measured during the baseline assessment using chest radiography, computed tomography (CT) scans, or magnetic resonance imaging (MRI) scans (when clinically indicated). During the study, medical history and physical examination results, vital signs, ECOG PS scores, CBCs, and blood chemistries were monitored weekly. Tumor responses were assessed using chest radiography, CT, or MRI (when clinically indicated) at every cycle until disease progression. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.0 [20]. A response of >4 weeks duration was considered a complete response (CR) or a partial response (PR) and a response of >6 weeks from the initiation of chemotherapy was considered stable disease (SD). Clinical response data were confirmed by central review.

Toxicities were assessed according to the National Cancer Institute-Common Toxicity Criteria, version 3.0.

The progression-free survival (PFS) was defined as the time from the date of enrollment to the date of documented progression or death from any cause and was censored at the date of the last follow-up visit for surviving patients who had not progressed. The overall survival (OS) time was defined as the time from the date of enrollment to the date of death or last follow-up. Data for patients without any events were censored on the last date with a nonevent status.

Statistical Analysis

The primary endpoint was the disease control rate (DCR), defined as the proportion of patients whose best response was a CR, a PR, or SD among all per-protocol patients. Sample size was determined according to the one-arm binomial design devised by the Southwestern Oncology Group. Assuming that a DCR of 50% in eligible patients indicates potential usefulness, whereas a DCR of 30% is the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.20$, the estimated accrual number was 37 patients. Allowing for a patient ineligibility rate of 10%, we planned on enrolling 40 patients in the study. Secondary endpoints were the OS, PFS, objective response rate (ORR), and

toxicity profiles. Survival curves were estimated using the Kaplan–Meier method. Statistical analyses were performed using JMP 10 (SAS Institute Inc., Cary, NC).

This study is registered with the University Hospital Medical Information Network (UMIN), number UMIN C000002306.

Results

Patient Characteristics

From August 2009 to May 2011, 41 patients were enrolled from 10 participating institutions. Patient characteristics are summarized in Table 1. The median age was 66 years (range, 43–74 years), 70.7% of patients were male, and most patients (97.6%) had a good ECOG PS score of 0–1. Histologic analysis revealed that 30 patients (73.2%) had adenocarcinoma and eight patients (19.5%) had squamous cell carcinoma. Seven patients (17.1%) were positive and 26 patients (63.4%) were negative for the *EGFR* mutation. Twenty-six patients (63.4%) received amrubicin as a third-line therapy and 15 patients (36.6%) received the drug as a fourth-line therapy.

Seven patients (17.1%) received thoracic surgery and nine patients (22.0%) received thoracic radiotherapy. Table 2 shows the content of prior therapeutic regimens. All patients had received a platinum-containing doublet regimen as a first- or second-line therapy. The regimens used in first-line therapy were as follows: platinum-containing doublets in 38 patients (92.7%), a single agent in two patients (4.9%), and gefitinib in one patient (2.4%). The regimens used in second-line therapy were as follows: a single agent in 21 patients (51.2%), platinum-containing doublets in 13 patients (31.7%), nonplatinum doublets in four patients (9.8%), and gefitinib in three patients (7.3%). The regimens used in third-line therapy were as follows: platinum-containing doublets in six patients (14.6%), a single agent in six patients (14.6%), and nonplatinum doublets in three patients (7.3%). Of the seven patients harboring *EGFR* mutations, three had not received EGFR TKIs before enrollment into this study because of patient refusal or later confirmation of the *EGFR* mutation.

Treatment Administered

The median number of treatment cycles was two (range, 1–9 cycles). In all, 30 (73.2%) patients completed at least two cycles of treatment and 109 treatment cycles in total were delivered overall. The mean relative dose intensity of amrubicin was 91.1%. A reduction in the amrubicin dose was necessary, according to the study protocol, in eight cycles (7.3% of the total cycles). All patients received the first cycle of amrubicin in an inpatient setting to check the safety of administration, and most patients received further cycles of amrubicin in an outpatient setting. Subsequent treatment delay was observed in 29 of 109 cycles (26.6%). The primary reasons for dose reduction were grade 4 neutropenia (four of all cycles), febrile neutropenia (three of all cycles), and grade 3 headache (one of all cycles). Treatment was discontinued in 11 patients after the first cycle and in 10 patients after the second cycle; reasons for discontinuation included progressive disease (24 patients), toxicity (six patients), completing the scheduled treatment (four patients), patient refusal (two patients), and physician decision (two patients). Following the protocol treatment, 23 (56%) patients eventually received subsequent therapy: nine (22%) received a single agent, nine (22%) received EGFR TKIs, three (7%) received platinum-containing doublets, and two (5%) received nonplatinum doublets.

Table 1. Patient characteristics

Characteristic	*n* of patients
Enrolled patients	41
Age, yrs	
Median	66
Range	43–74
Gender	
Male	29
Female	12
ECOG performance status score	
0	16
1	24
2	1
Histological type	
Adenocarcinoma	30
Squamous cell carcinoma	8
Large cell carcinoma	2
Other (not specified)	1
EGFR mutation status	
Positive	7
Negative	26
Unknown	8
n of prior treatment regimens	
2	26
3	15

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Response and Survival

Among the 41 assessable patients, there were four PRs and no case of CR, for an overall response rate of 9.8% (95% confidence interval [CI], 0.6%–18.8%) (Table 3). Twenty-one patients (51.2%) had SD, yielding an overall DCR of 61.0% (95% CI, 46.0%–75.9%). Fifteen patients had progressive disease as their best response and the response of one patient could not be confirmed as a result of receipt of subsequent chemotherapy before response evaluation. The lower end of the 95% CI was thus higher than the threshold DCR of 30%, and the primary endpoint was met. We found no significant difference in the ORR or DCR among gender, age, tumor histology, *EGFR* mutation status, or treatment line, except for the DCR and *EGFR* mutation status—the DCR was 100% in seven patients with an *EGFR* mutation, 46.2% in 26 patients with wild-type *EGFR*, and 85.7% in seven patients with an unknown *EGFR* status ($p = .012$).

Of the 41 patients, 13 were alive as of May 2012 (>1 year after the last patient was enrolled). With a median follow-up time of 12.6 months, the median PFS and median survival time (MST) for all enrolled patients were 3.0 months (95% CI, 2.0–4.1 months) and 12.6 months (95% CI, 6.8–19.3 months), respectively (Figs. 1 and 2). The 1-year survival rate was 53.7% (95% CI, 38.4%–68.9%).

Table 2. Characteristics of prior first-line, second-line, and third-line therapies

Characteristic	First-line therapy	Second-line therapy	Third-line therapy
Total	41	41	15
Treatment regimen			
Doublet	38	17	9
Platinum-based doublets	38	13	6
Paclitaxel based	15	5	2
Gemcitabine based	9	1	1
Vinorelbine based	5	0	0
Docetaxel based	4	2	0
Pemetrexed based	3	4	2
Other	2	1	1
Nonplatinum doublets	0	4	3
Single agent	2	21	6
Docetaxel	2	15	2
Pemetrexed	0	6	2
Vinorelbine	0	0	2
Gefitinib	1	3	0

Table 3. Overall response rate for patients treated with amrubicin as determined by central review

Response	*n* of patients	%	95% CI
Complete response	0	0	
Partial response	4	9.8	
Stable disease	21	51.2	
Progressive disease	15	36.6	
Not evaluable	1	2.4	
Overall response rate	4	9.8	0.6%–18.8%
Disease control rate	25	61.0	46.0%–75.9%

Abbreviation: CI, confidence interval.

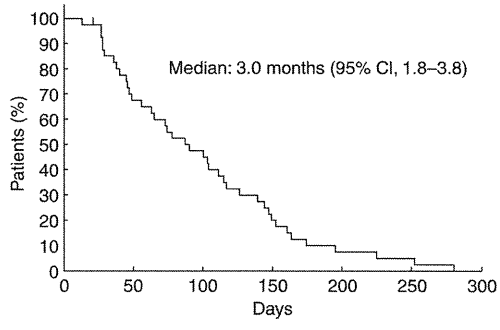

Figure 1. Kaplan–Meier analysis of progression-free survival for all 41 treated patients.
Abbreviation: CI, confidence interval.

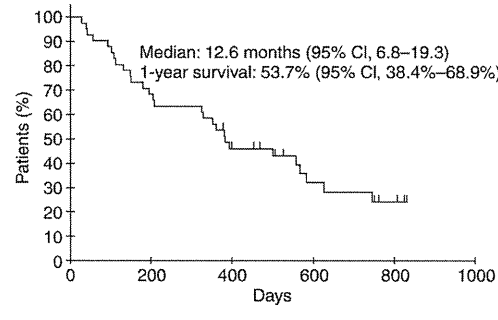

Figure 2. Kaplan–Meier analysis of overall survival for all 41 treated patients.
Abbreviation: CI, confidence interval.

Toxicity

All 41 treated patients were assessed for toxicity. Table 4 summarizes the hematological and nonhematological toxicities. With regard to hematological toxicities, 68% of patients experienced grade 3 or 4 neutropenia and 17% developed febrile neutropenia. Nineteen patients (46%) were treated with G-CSF for 1–11 days during the first treatment cycle because of neutropenia. Although no serious hematologic events were observed, grade 3 or 4 thrombocytopenia was observed in five patients (12%; one received a platelet transfusion) and anemia was observed in five patients (12%; two received a packed RBC transfusion). The most common nonhematologic toxicities of grade 3 or 4 were anorexia (12%), infection (10%), nausea or vomiting (10%), diarrhea (2%), stomatitis (2%), and pneumonitis (2%). Most nonhematologic toxicities were mild and reversible. Neither cardiac toxicity nor treatment-related deaths were observed in this study.

Discussion

This is the first prospective phase II study designed to evaluate the efficacy and safety of a cytotoxic agent as a third- or