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address the majority of older adults in first-world countries, and we believe that we have succeeded. In our data set, we find that the Mini-Cog functions significantly better than the MMSE with standard cutpoints in subjects with low education and literacy. It was not designed to function optimally in populations broadly characterized by extremely low levels of education or literacy. In such settings, informant-based screening or individualized function-based screening might do better than any cognitive screen that relies on standard neuropsychological paradigms. To our knowledge, the jury is still out, and much remains to be done.

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CARBOCISTEINE REDUCES FREQUENCY OF COMMON COLDS AND EXACERBATIONS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

To the Editor: Various kind of viruses, including rhinovirus and influenza virus, have been reported to cause chronic obstructive pulmonary disease (COPD) exacerbations.[1] Mucolytic drugs prevent acute exacerbations of chronic obstructive bronchitis.[2] Mucolytic drugs, including carbocisteine, have various effects, such as the reduction of elastic modules of mucus and improvement of mucociliary transport.[3] Therefore, it is conceivable that mucolytic drugs may modulate the function of airway epithelial cells, including the expression of intercellular adhesion molecule-1, a receptor for major rhinoviruses that are the most commonly implicated pathogens of common colds,[4] although the effects of carbocisteine have not been studied on the prevention of the common cold in patients with COPD.

In the present study, a prospective, randomized, double-blind, controlled trial was performed to examine the effects of carbocisteine on the frequency of common colds and exacerbations in patients with COPD. Patients diagnosed with COPD[5] were enrolled and treated with sustained-release theophylline, inhaled oxitropium bromide, inhaled β_2-agonist, or a combination of these but did not receive inhaled or oral corticosteroids. One hundred fifty-six patients were randomly assigned to receive carbocisteine therapy (1,500 mg/d, 78 patients, carbocisteine group) or placebo therapy with tablets of lactose (1,500 mg/d, 78 patients, control group) until the end of the study, between October 2001 and June 2005 at the Tohoku University Hospital, Sendai, Japan. Ten symptoms of upper respiratory tract infections were recorded in each patient, and common cold was defined as a total symptom score of greater than 5, as described previously.[6] A COPD exacerbation was defined as an acute and sustained worsening of COPD symptoms requiring changes to regular treatment, as previously described.[7] The primary endpoints of this study were to compare the rate and number of common colds and exacerbations of the carbocisteine group and the control group. The rate and number of common colds and acute exacerbations of COPD were observed for 12 months. It was estimated that 50 patients per group needed to be enrolled on the basis of experimental-treatment group to confer a power of 80% for a two-sided 0.05 level by sample size analysis.[8] Actual accrual was 78 eligible patients in each group. The sample sizes for the two groups were thought to be sufficient to demonstrate the primary endpoints in the present study. Significance was accepted at $P < .05$. The Tohoku University Ethics Committee approved the study, and written informed consent was obtained from all patients.

None of the patients in either group died or had any apparent adverse effects from carbocisteine therapy during the study period. None of the 156 patients with COPD were lost to follow-up, and all were analyzable. Age, sex, smoking history, stage of COPD, and lung function test were matched between the two groups (Table 1). The mean number ± standard deviation of common colds for 12 months was significantly lower in the carbocysteine group (1.69 ± 0.18 per person) than in the control group (3.14 ± 0.35 per person; $P < .001$, Student t test) (Table 1). The use of carbocisteine was closely associated with a lower frequency of development of common colds more than twice per year in patients with COPD (relative risk = 0.4, 95% confidence interval (CI) = 0.2–0.8, $P = .009$). The number of exacerbations for 12 months was also significantly lower in the carbocisteine group than in the control group ($P < .001$, Student t test) (Table 1). One hundred eight COPD exacerbations related to 245 common colds (44%) occurred in the control group and 42 exacerbations related

Table 1. Subject Characteristics and Frequency of Common Colds and Exacerbations in Patients with Chronic Obstructive Pulmonary Disorder (COPD)

Characteristic	Control Group (n = 78)	Carbocisteine Group (n = 78)	Odds Ratio (95% Confidence Interval)	*P*-value
Age, mean ± SE	72.8 ± 1.0	72.5 ± 1.0		.82
Sex, n				
Male	67	66		.82
Female	11	12		
Smoking history (pack-year), mean ± SE	46.6 ± 3.1	42.1 ± 3.0		.29
COPD stage, n				
I	23	28		.39
II	43	42		.87
III	12	8		.34
Pulmonary function, mean ± SE				
FVC, L	2.19 ± 0.03	2.19 ± 0.03		.99
FEV1, L/s	1.41 ± 0.05	1.41 ± 0.05		.99
FEV1/FVC, %	64.4 ± 2.2	64.4 ± 2.2		.99
FEV1, % predicted	61.5 ± 2.2	61.4 ± 2.1		.98
Total common colds/year, n	245	132		
Mean common colds/year, mean ± SE	3.14 ± 0.35	1.69 ± 0.18		<.001
Total patients with ≥2 common colds/year, n (%)	53 (68)	35 (45)	0.4 (0.2–0.8)	.009
Total exacerbations/year, n	108	42		
Mean exacerbations/year, mean ± SE	1.38 ± 0.20	0.54 ± 0.11		<.001
Total patients with ≥1 exacerbations/year, n (%)	47 (60)	28 (36)	0.3 (0.2–0.7)	.002

SE = standard error; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second.

to 132 common colds (32%) in the carbocisteine group. The relative risk of experiencing an exacerbation in the carbocisteine group compared with that in the control group was 0.3 (95% CI = 0.2–0.7, $P = .002$).

In this study, the number of common colds and exacerbations was significantly lower in the carbocisteine group than in the control group. The lower rate of COPD exacerbations observed in this study is consistent with a previous report using carbocisteine.[2] The mucolytic drug ambroxol inhibits influenza virus proliferation,[9] although the inhibitory effects of carbocisteine on the influenza virus and rhinovirus, major pathogens of COPD exacerbations, were not studied in the present study.[1] Alternatively, another mucolytic drug, S-carboxymethylcysteine, inhibits neutrophil activation, which plays a key role in COPD exacerbations.[10] These antiviral and antiinflammatory effects of carbocisteine might be associated with the prevention of common colds and exacerbations in patients with COPD in the present study. Carbocisteine may have beneficial effects on the prevention of common colds and exacerbations in patients with COPD.

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OUTCOMES OF OLDER PEOPLE ADMITTED TO POSTACUTE FACILITIES WITH DELIRIUM

To the Editor: As emphasized by Marcantonio et al. in their article recently published in the *Journal of the American Geriatrics Society*,[1] the literature on delirium in postacute facilities is limited. We would contribute to this topic with personal data showing the clinical outcomes of older people admitted to our rehabilitation and aged care unit (RACU) in Cremona, Italy. The RACU is a 40-bed ward devoted to the rehabilitation of postacute (e.g., stroke, hip fracture, hip or knee arthroplasty, cardiorespiratory) or chronic patients with gait and balance dysfunctions. Upon admission, patients routinely receive a geriatric multidimensional assessment, including Confusion Assessment Method (CAM), Mini-Mental State Examination (MMSE), Charlson Index, and Barthel Index. The Barthel Index is also scored with reference to 1 month before admission and at discharge. A progress note in the medical record documents geriatric (fall and skin pressure ulcers) and medical (cardiovascular, respiratory, urinary, iatrogenic) complications. At 12 months, institutionalization and deaths are investigated using surrogate interviews. From January 2002 to June 2005, 1,586 elderly subjects were consecutively admitted to the RACU. Of these, 214 (15.6%) developed delirium (Table 1).

Table 1 shows that outcomes are comparable in many aspects with those of Marcantonio et al.'s study. First, the prevalence of delirium is similar in the two populations; when considering the final population of Marcantonio et al.'s study (1,248 subjects of the 1,623 eligible for the analysis) the prevalence of full delirium was 15%, whereas it was 15.6% in our study. Second, like in our population, all delirious subjects were older than those without delirium, and sex did not differ across groups. Third, subjects with delirium were more likely to experience geriatric and medical complications. Fourth, RACU admission was longer than 30 days for 32.6% of our delirious subjects and for 36% in Marcantonio et al.'s study. Nevertheless, despite these similarities, there are many aspects that clearly differ between the studies and deserve comments. First, we did not measure subsyndromal delirium. Second, although chronic conditions were more frequent in our population (see Charlson Index), mortality was unexpectedly lower (21.8% at 12 months compared with 25.0% at 6 months

Table 1. Clinical Characteristics of 1,586 Elderly Subjects Consecutively Admitted to a Rehabilitation and Aged Care Unit (RACU) Stratified by Occurrence of Delirium

Characteristic	Delirium (n = 214)	No Delirium (n = 1,372)
Age, mean ± SD	82.2 ± 7.0	78.4 ± 7.0
Female, n (%)*	158 (73.8)	1,027 (74.9)
Charlson Index, mean ± SD	3.3 ± 2.0	2.6 ± 2.1
Mini-Mental State Examination score, mean ± SD	18.0 ± 7.0	23.7 ± 5.4
Barthel Index, mean ± SD		
1 month before admission	75.2 ± 24.5	83.6 ± 20.5
On admission	34.6 ± 24.3	61.7 ± 25.7
At discharge	59.4 ± 27.8	79.9 ± 22.1
Any geriatric complication, mean ± SD	0.9 ± 0.9	0.3 ± 0.5
>1 fall, n (%)	31 (14.5)	69 (5.0)
Pressure ulcers, n (%)	14 (6.5)	9 (0.7)
New medical complications, n (%)	137 (64.4)	273 (19.9)
Cardiovascular†	13 (6.1)	39 (2.8)
Respiratory	66 (30.8)	119 (8.7)
Urinary	44 (20.6)	99 (7.2)
Iatrogenic	14 (6.5)	16 (1.2)
Remained in RACU for ≥ 30 days, n (%)	72 (32.6)	209 (15.1)
Discharged to the community, n (%)‡	175 (79.5)	1,288 (92.9)
Institutionalized at 12 months	23 (24.5)	53 (7.3)
Dead at 12 months	26 (21.8)	60 (7.7)

*$P = .75$.
†$P = .01$.
‡Data refer to 914 subjects, 122 (13.3%) of whom had delirium.
SD = standard deviation.

standard treatments.[10] Lately, it has been shown that cyclophosphamide, doxorubicin, vincristine, and prednisone, with the addition of rituximab, is the standard treatment for non-Hodgkin's lymphoma in older people.

In conclusion, despite the perceived barriers to including elderly cancer patients in clinical trials, there are few data to support excluding them. The increasing use of a complete geriatric assessment can lead to a more individualized patient treatment plan. Furthermore, the enormous advances in supportive treatments over recent years enable adverse effects to be minimized. Moreover, the implementation of prospective trials is strongly recommended to assess properly the quality of life of elderly patients undergoing chemotherapy. In this way, it could be possible to counteract an unjustified "ageism": a prejudice that denies opportunities of treatment or even cure for patients that, as far as we know, may have the same chance as younger patients.

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ARTERIAL CARBOXYHEMOGLOBIN CONCENTRATIONS AS A PREDICTOR OF CHEMOSENSITIVITY IN ELDERLY PATIENTS WITH ADVANCED LUNG CANCER

To the Editor: Because the response to anticancer drugs is different in elderly patients with lung cancer, a reliable and simple method[1] to predict the response to chemotherapy is needed. Arterial blood carboxyhemoglobin concentration (Hb-CO) is a useful biomarker of disease activity in inflammatory pulmonary diseases,[2–5] although it has not been reported as a predictor of response to chemotherapy in advanced lung cancer.

One hundred one elderly patients (mean age ± SE = 70.4 ± 1.1) with advanced lung cancer treated with chemotherapy were studied. Thirty-five of 101 patients had small-cell lung cancer (SCLC), and 66 had non-small-cell lung cancer (NSCLC). The characteristics of the patients are shown in Table 1. Patients with SCLC were treated with cisplatin 80 mg/m^2 at Day 1 and etoposide 100 mg/m^2 at Days 1–3 every 3 weeks for a maximum of four cycles. Patients with NSCLC were treated with mitomycin 8 mg/m^2 at Day 1, vinorelbine 25 mg/m^2 at Days 1 and 8, and cisplatin 80 mg/m^2 at Day 1) or gemcitabine 1,000 mg/m^2 at Days 1 and 8 and docetaxel 60 mg/m^2 at Day 1 every 3 weeks for a maximum of four cycles. A chest computed tomography scan was performed before chemotherapy and after the second and fourth cycles of chemotherapy to estimate the effect of chemotherapy on tumor volume. An attending oncologist evaluated response to the chemotherapy according to the criteria of the World Health Organization.[6] Hb-CO was measured using a spectrophotometer[2–5] before chemotherapy and at Days 4 and 21 of the first cycle of chemotherapy. Current smokers were excluded by measuring urinary cotinine concentrations.[2,4] The patients were divided into two subgroups: patients with high and low maximum changes in Hb-CO during chemotherapy relative to an arbitrary cutoff value (0.3%) discriminating the responder from the nonresponder in chemotherapy, which was determined using receiver operating characteristic curve analysis with ROCKIT (Windows 95, version 0.9.1 beta, Microsoft, Corp., Redmond, WA). The Tohoku University Ethics Committee approved this study, and informed consent was obtained from each subject.

The response rate was 80% in patients with SCLC and 38% in those with NSCLC. In responder patients with SCLC and NSCLC, Hb-CO increased significantly,

Table 1. Characteristics of Patients with High or Low Carboxyhemoglobin (Hb-CO) Changes

Characteristic	Hb-CO Change					
	Small Cell Lung Cancer			Non-Small Cell Lung Cancer		
	Low (n = 9)	High (n = 26)	*P*-value	Low (n = 42)	High (n = 24)	*P*-value
Age, median (range)	71 (61–78)	71 (55–80)	NS	68 (54–84)	70 (55–82)	NS
Male/female, n	9/0	21/5	NS	31/11	19/5	NS
Smoking history, n			NS			NS
Exsmoker	9	24		37	22	
Nonsmoker	0	2		5	2	
Stage, n			NS			<.01
IIIB	2	14		6	13	
IV	7	12		36	11	
Cell type, n			—			NS
Small cell	9	26		—	—	
Squamous cell	—	—		17	9	
Adenocarcinoma	—	—		19	15	
Large cell	—	—		6	0	
Chemotherapy, n			—			<.05
Cisplatin+etoposide	9	26		—	—	
Mitomycin+vinorelbine+cisplatin	—	—		22	20	
Gemcitabine+docetaxel	—	—		20	4	
Hb-CO before chemotherapy, %, mean ± SE	0.99 ± 0.10	0.61 ± 0.03	<.001	0.79 ± 0.03	0.64 ± 0.04	<.01
Maximum change in Hb-CO during chemotherapy, %, mean ± SE	0.08 ± 0.03	0.55 ± 0.04	<.001	0.06 ± 0.01	0.46 ± 0.04	<.001
Tumor shrinkage, cm^3, mean ± SE	−1.78 ± 2.48	15.23 ± 2.42	<.001	−3.00 ± 1.14	17.16 ± 2.49	<.001
Chemosensitivity			<.001			<.001
Responder	2	26		1	24	
Nonresponder	7	0		41	0	

NS = nonsignificant; SE = standard error.

achieved maximum change at Day 4 of the first cycle of chemotherapy, and then returned to baseline. In contrast, in nonresponder patients with SCLC and NSCLC, Hb-CO did not increase during chemotherapy. Hb-CO before chemotherapy in responders to the chemotherapy was significantly lower than in nonresponders with SCLC ($P<.001$) and NSCLC ($P<.01$) (Student t test). Twenty-six of 28 responding patients with SCLC and 24 of 25 responding patients with NSCLC were categorized as patients with high Hb-CO changes. The response rate of patients with high Hb-CO changes was significantly higher than that of patients with low Hb-CO changes, regardless of whether they had SCLC or NSCLC ($P<.001$ for both; chi-square test) (Table 1). Hb-CO correlated significantly with tumor size in patients with SCLC (correlation coefficient (r) = 0.83, $P<.001$) and those with NSCLC ($r = 0.27$, $P<.05$) before chemotherapy. Maximum increases in Hb-CO at Day 4 of the first cycle of chemotherapy were significantly associated with the response to the chemotherapy in patients with SCLC (regression coefficient (RC) = 0.70 (95% confidence interval (CI) = 0.44–0.96, $P<.001$)) and those with NSCLC (RC = 1.52, 95% CI = 1.24–1.80, $P<.001$) (multiple regression analysis). For the distinction between nonresponders and responders to chemotherapy, the cutoff value of 0.3% of the maximum increases in the Hb-CO during chemotherapy in patients with SCLC yielded a sensitivity of 95.9% and a specificity of 95.0% and that in patients with NSCLC yielded a sensitivity of 96.4% and a specificity of 97.0%.

The positive correlation between Hb-CO before chemotherapy and tumor volume in this study is consistent with a previous report.[7] A hypoxic condition in a solid tumor induces heme oxygenase-1 (HO-1) via an increase in hypoxia-inducible factor-1, which endogenously produces carbon monoxide.[8,9] Furthermore, resistance to an anticancer drug increases with tumor volume, because the increased hypoxia in tumors induces p-glycoprotein related to resistance to anticancer drugs.[8] Therefore, the increase in Hb-CO before chemotherapy may be associated with low chemosensitivity in lung cancer. A transient increase in Hb-CO during chemotherapy in responders was demonstrated in the present study. The decrease in tumor volume after chemotherapy may be associated with the induction of HO-1 in cancer tissue through generation of reactive oxygen species from apoptotic cancer cells,[9,10] but the precise mechanism is unknown.

In summary, arterial Hb-CO before chemotherapy in patients with SCLC and increases in arterial Hb-CO at Day 4 of the first cycle of chemotherapy in patients with SCLC and NSCLC may be a predictor of chemosensitivity.

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EVIDENCE-BASED PRESCRIBING OF ANTIRESORPTIVE THERAPY FOR FEMALE NURSING HOME RESIDENTS WITH OSTEOPOROSIS: HOW GOOD IS THE EVIDENCE?

To the Editor: Bone health in nursing home residents and postmenopausal osteoporosis are important.[1,2] Dr. Jachna et al.[3] found that only 20% of nursing facility residents received antiresorptive therapy, which was considered to be underused.[3] Two interesting articles among others in the editorial were cited to support the evidence-based prescribing of antiresorptive therapy for nursing home women and therefore to improve the underuse of antiresorptive therapy.[4] In the first study cited,[5] 68% of participants were living in continuing-care retirement communities, 12% in retirement communities, 12% in skilled-care nursing homes and residential-care facilities, and 8% in congregate-care facilities. Because the majority of participants were not nursing home residents, the results from this study[5] might not be applicable to the nursing home setting. Searching PubMed between 1997 and 2005 found no single randomized risedronate trial conducted only in nursing homes. Based on the meta-analysis of the Cochrane Review in the second study cited,[6] the editorial estimated that taking risedronate for 2 years would prevent 55 vertebral (number needed to treat = 16) and 25 nonvertebral (number needed to treat = 35) fractures,[4] but the Jadad 5-point scale used for the internal validity of eight randomized risedronate trials of postmenopausal osteoporosis in the non-nursing home setting from the meta-analysis in the second cited study was between 1 of 5 and 5 of 5.[6] Median Jadad 5-point score was 3 (range 1–5). Using Jadad score to assess the quality of randomized risedronate trials might be unfamiliar to the majority of practicing physicians. Therefore, major items for internal validity of six randomized risedronate trials included in the meta-analysis in the second study cited[6] (one trial published as an abstract and another in the symposium were excluded) are listed in Table 1. High dropouts could reduce the internal validity of these trials. In addition, most of these trials did not provide methods of randomization and allocation concealment, which is consistent with previous findings.[7] Poor quality of research has been a major concern.[7,8] The low quality of trials included in the meta-analyses could lead to significant exaggeration of treatment

Table 1. Selected Internal Validity Indicators of Randomized Risedronate Trials (N = 6)

Indicators	Value
Reporting power calculation, n (%)	3 (50.0)
Described as randomized, n (%)	6 (100.0)
Reporting method of randomization, n (%)	1 (16.7)
Reporting method of allocation concealment, n (%)	1 (16.7)
Described as double blind, n (%)	6 (100.0)
Reporting dropouts, n (%)	6 (100.0)
Dropouts, n, median (range)	280 (15–4,654)
Dropout rate, %, median (range)	37.6 (13.5–49.9)
Jadad score, median (range)*	3 (3–5)

*From the original study.[6] Jadad score is between 0 and 5.

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ORIGINAL REPORT

Randomized Phase II Trial Comparing Nitroglycerin Plus Vinorelbine and Cisplatin With Vinorelbine and Cisplatin Alone in Previously Untreated Stage IIIB/IV Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
To investigate the efficacy and safety of nitroglycerin plus vinorelbine and cisplatin in patients with previously untreated stage IIIB/IV non–small-cell lung cancer (NSCLC) as the experimental arm for the next phase III trial.

Patients and Methods
One hundred twenty patients with stage IIIB/IV NSCLC were randomly assigned to vinorelbine 25 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1, with transdermally applied nitroglycerin (25 mg/patient daily for 5 days; arm A) or with placebo patch (arm B) every 3 weeks for a maximum of four cycles in a double-blind and controlled trial. Primary efficacy end points were the best confirmed response rate and time to disease progression (TTP).

Results
The response rate in arm A (72%; 43 of 60 patients) was significantly higher than that for patients in arm B (42%; 25 of 60 patients; $P < .001$). Median TTP in arm A was longer than that in arm B (327 *v* 185 days). No severe adverse effect was recognized for either arm. The rate of grade 1 to 2 headache in arm A (30%; 18 of 60 patients) was significantly higher than that in arm B (2%; one of 60 patients; $P < .001$, χ^2 test).

Conclusion
Use of nitroglycerin combined with vinorelbine and cisplatin may improve overall response and TTP in patients with stage IIIB/IV NSCLC. The arm A regimen is being evaluated in a large phase III trial.

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INTRODUCTION

Low levels of oxygenation due to relative vascular insufficiency have been demonstrated to exist in solid cancers but not in normal tissues,[1-4] and hypoxic conditions in solid cancers are associated with resistance to cancer therapy.[5-7] Hypoxia-inducible factor-1 (HIF-1) activates the transcription of many genes that code for proteins involved in angiogenesis, cell growth, metastasis, and resistance to chemotherapy.[8-12] Hypoxia in solid cancers promotes stabilization of HIF-1,[13] and anticancer therapy to inhibit HIF-1 has been reported recently.[12,14,15] The administration of nitric oxide (NO)–donating drugs decreased hypoxia-induced resistance to anticancer drugs in cancer cell lines.[16] However, the effects of NO and NO-donating drugs on inhibition of HIF-1 activation during hypoxia remains controversial.[17-20]

Isosorbide dinitrate and inducible NO synthase gene transfer have various effects on tumor tissue and cells, including augmentation of oxygen pressure in tumor tissue through an increase in blood flow[21]; cytotoxicity in tumor cells[22,23]; programmed cell death that is dependent on position in the cell cycle[24]; and p53 protein activation, apoptosis, and growth inhibition in cancer cells.[20,25] In contrast, NO promotes tumor angiogenesis and tumor progression.[26,27]

A variety of anticancer drugs have been developed for treatment of lung cancer and have contributed to prolonged survival.[28,29] However, even

third-generation regimens such as vinorelbine plus cisplatin (VC) result in survival rates of only 26% to 36% at 1 year and in median overall survival of 8 to 9 months among patients with advanced non–small-cell lung cancer (NSCLC) and good performance status (PS).[30-32]

In our preliminary survey, the response rate to chemotherapy using VC was significantly higher in patients with lung cancer and angina pectoris treated with nitroglycerin than in patients with lung cancer who did not have angina pectoris and did not use nitroglycerin treatment (unpublished data). However, the beneficial effects of NO-donating drugs on response to chemotherapy and on time to progression (TTP) in patients with lung cancer have not been reported to date.

PATIENTS AND METHODS

Patient Characteristics

A total of 193 patients with inoperable advanced NSCLC were recruited onto this study, and 120 of 193 patients fit the 15 inclusion criteria (Table 1). Grounds for exclusion at enrollment for 73 of 193 recruited patients were as follows: use of vasodilators including antihypertensive drugs in 41 patients; Eastern Cooperative Oncology Group[33] PS ≥ 2 in 17 patients; brain metastasis in 12 patients; renal, hematologic, or cardiac dysfunction in three patients.

The 120 eligible patients were randomly assigned to receive VC with or without nitroglycerin during chemotherapy in a double-blind phase II trial at the Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine (Sendai, Japan), and at the Division of Internal Medicine, Furukawa City Hospital (Furukawa, Miyagi Prefecture, Japan). Enrollment took place between April 2001 and February 2003. The random allocation sequence was generated by a random-number table at the coordinating center at the Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine.

PS was rated using the Eastern Cooperative Oncology Group scale.[33] Staging of NSCLC was determined using computed tomography (CT) scans of the brain, chest, and abdomen, positron emission tomography, gallium-67 citrate scintigraphy, and technetium-99m scintigraphy of the bone. Stage was defined using the revised lung cancer staging system of the American Joint Committee on Cancer.[34] Participant characteristics are listed in Table 2.

Table 1. Enrollment Criteria

The diagnosis of lung cancer was confirmed with histologic or cytologic examination
Age ≥ 40 years old
No treatment with a vasodilator such as calcium channel blockers
Stage IIIB or stage IV
No prior chemotherapy or radiotherapy
A measurable or evaluable tumor lesion according to WHO criteria
Good performance status: a performance status of 0-1 according to the ECOG scale
Without brain metastasis
Adequate renal function (calculated creatinine clearance of > 50 mL/min)
Adequate hepatic function (serum bilirubin, ALT, and AST < 2× ULN)
Adequate hematologic function (neutrophil count > 2,000/mL, hemoglobin > 10 g/dL, platelet count ≥ 100,000/mL)
Adequate cardiac function (cardiothoracic ratio < 55%)
Informed consent to receive chemotherapy and attend this study was obtained
Scheduled treatment with chemotherapy and without radiotherapy
No ischemic heart diseases

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal.

Table 2. Characteristics of the Patients With Non–Small-Cell Lung Cancer

Characteristic	Arm A, With Nitroglycerin (n = 60)		Arm B, Without Nitroglycerin (n = 60)		P
	Value	No. of Patients	Value	No. of Patients	
Age, years					
Median	64		64		.63
Range	40-75		41-75		
Sex					
Male		53		52	.78
Female		7		8	
Performance status					
0		44		42	.69
1		16		18	
Smoking history, pack-year					
Median	46		47		.81
Range	0-135		0-125		
Nonsmoker		12		15	.64
Ex-smoker		17		13	
Current smoker		31		32	
Cell type					
Squamous cell		29		23	.15
Adenocarcinoma		27		36	
Large cell		4		1	
Staging					
IIIB		26		22	.46
IV		34		38	

Chemotherapy Treatment

Of the 120 patients, 60 were treated with VC (vinorelbine 25 mg/m^2 on days 1 and 8; cisplatin 80 mg/m^2 on day 1) every 3 weeks for a maximum of four cycles with transdermally applied nitroglycerin (25 mg/patient daily for 5 days between 3 days before the start of each cycle of chemotherapy and cycle day 2; arm A). Nitroglycerin transdermal patches (5 to 25 mg/patient daily) are widely and safely used in treatment of coronary artery disease and heart failure.[35] Therefore, we used 25 mg/patient nitroglycerin transdermal patches daily as the NO donor. The other 60 patients were treated with VC every 3 weeks for a maximum of four cycles with placebo patches (arm B). Nitroglycerin was used only with first-line chemotherapy.

Change in Chemotherapy Timing and Dose Adjustments

Drug administration was postponed for a maximum of 2 weeks if there was incomplete hematologic recovery on day 22 (leukocytes < 2,000/mL and/or platelets < 100,000/mL) or there was persistent grade 2 or more nonhematologic toxicity according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 2.0.[36] Dosage of anticancer drugs for the subsequent course was reduced to 80% in the event of grade 3 to 4 nonhematologic toxicity (except nausea, vomiting, and headache). Treatment was stopped if the same toxicity occurred with chemotherapy at a reduced dose level. Nonsteroidal anti-inflammatory drugs were used if nitroglycerin-induced headache occurred.

Estimation of Response to Treatment and Follow-Up Assessments

To assess nitroglycerin effects on response to chemotherapy, we compared identifiable tumor sizes with a chest CT scan after the finish of the second and fourth cycles of chemotherapy. Response rate was evaluated by two independent radiologists and an independent oncologist according to WHO criteria.[37] Patients were categorized as responders when they experienced either a partial response or a complete response. Patients with no change or progressive disease were categorized as nonresponders.

Once patients came off protocol treatment, they were evaluated by physical examination every 4 weeks and by CBC, biochemical tests, and chest

radiograph every 3 months. If necessary, CT scans of the brain, chest, or abdomen were appropriately performed to assess disease progression. CT scans were reviewed by two independent radiologists and an independent oncologist to confirm disease progression.

Treatment Toxicity

Toxic effects of anticancer drugs were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 2.0.[36]

Study Design and Sample Size

The primary efficacy end point was comparison of response rate and TTP between arms A and B. A secondary efficacy end point was overall survival. Efficacy analyses were based on an intent-to-treat analysis.

We estimated that we needed to enroll 54 patients per arm on the basis of an experimental-treatment group to confer a power of 80% for a two-sided .05-level test to detect an increase in 1-year progression-free probability of 26% (from 26% to 52%) in the pooled nitroglycerin-treated arm.[32,38] Actual accrual was 60 eligible patients and 56 assessable patients for both arms A and B (Fig 1). This is the report of an interim analysis; the final analysis is planned for 2 years from the end of accrual. This study was approved by the Tohoku University Ethics Committee and informed consent was obtained from each subject.

Measurements of Plasma Vascular Endothelial Growth Factor Levels

To study nitroglycerin effects on the HIF-1 pathway, we measured plasma levels of vascular endothelial growth factor (VEGF), which is regulated by HIF-1.[39] Plasma levels of VEGF were measured as previously described[40] before and after 3 days of treatment with transdermally applied nitroglycerin patches (arm A) or placebo patches (arm B).

Statistical Methods

For statistical analysis, age, sex, performance status, smoking history, cancer cell type, cancer staging, treatment delivery, anticancer drugs dose-intensity, adverse effects due to chemotherapy, and response rate were compared using Pearson's χ^2 contingency table analysis (or Fisher's exact probability test whenever appropriate) between arms A and B. Age and smoking history (pack-year) between arms A and B, and plasma VEGF levels before and after use of nitroglycerin in arm A and placebo patches in arm B were compared using the Student's t test. Factors associated with response rate such as age, sex, performance status, cancer cell type, cancer staging, and use of nitroglycerin during chemotherapy were calculated with logistic regression analysis. Relative risks (RRs) and 95% CIs were calculated to assess response rate.

TTP was defined as the time from date of random assignment to date of disease progression. The probability of remaining free of progression or of surviving was estimated using the Kaplan-Meier product-limit method. P values indicated the significance of differences between arms A and B by log-rank test. Overall survival was calculated from the date of random assignment to the date of death or a cutoff date for patients alive at the time of closure of the data set.

Multivariate analysis by Cox regression analysis was performed to assess the prognostic significance of several variables, including age, sex, performance status, cancer cell type, cancer staging, and use of nitroglycerin combined with anticancer drugs.

All statistical analyses in this study were carried out using the Stat View program (SAS Institute Inc, Cary, NC). Results of interim significance tests were not considered significant unless the P values were less than .001.

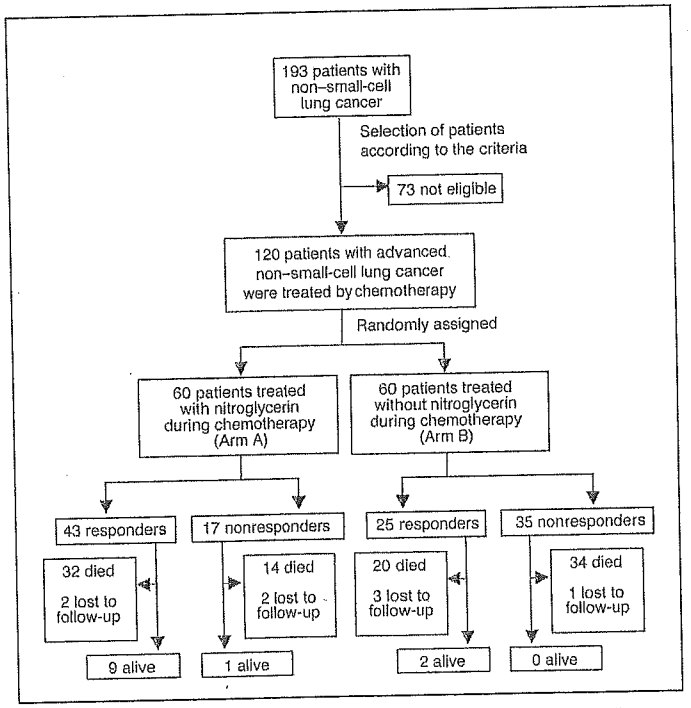

Fig 1. Trial profile. A total of 120 patients with advanced non–small-cell cancer were randomly assigned to chemotherapy with or without nitroglycerin and were observed to evaluate the effects of nitroglycerin combined with vinorelbine and cisplatin on response to chemotherapy and time to progression.

RESULTS

Patient Characteristics

There were no statistically significant differences in baseline characteristics between arms A and B (Table 2).

Chemotherapy Treatment

In arm A, 44 (73%) of 60 patients received all four courses of chemotherapy. Of the 44 patients, 17 received chemotherapy at the full prescribed dose, and 10 of 44 received chemotherapy without any modification of dose. Conversely, in arm B, 35 (58%) of 60 patients received all four courses of chemotherapy. Of those 35 patients, 16 received chemotherapy at the full prescribed dose and 12 of 35 received chemotherapy without any modification of dose. The mean number of chemotherapy courses was 3.52 for arm A and 3.27 for arm B. There were no significant differences between arms in dose of anticancer drugs or the number of chemotherapy courses (Table 3).

Treatment Toxicity

In first-line chemotherapy, the frequency of adverse effects grade ≥ 3 in arm A did not differ from that in arm B (Table 4).[36] The rate of grade 1 (15 of 60 patients) and grade 2 (3 of 60) headache in arm A (30%; 18 of 60) was significantly higher than that in arm B (2%; one of 60; $P < .001$, χ^2 test). However, there were no severe headaches of grade ≥ 3 in arm A. Conversely, grade 1 hypotension was observed in arm A (5%; three of 60). There was no severe hypotension of grade ≥ 3 in arm A during treatment with nitroglycerin.

There was a high rate of severe neutropenia in arm A (58%; 35 of 60) and arm B (57%; 34 of 60; Table 4). Furthermore, higher frequencies of persistent neutropenia on day 8 were observed in the fourth course in arm A (64%; 28 of 44) and in arm B (63%; 22 of 35). Therefore, the start timing of the fourth course of chemotherapy was postponed for some of the patients in arm A (48%; 21 of 44) and arm B (40%; 14 of 35).

Response Rate

Table 5 shows the response rate for arms A and B: the response rate in arm A (72%; 43 of 60 patients) was significantly higher than

Table 3. Treatment Delivery

Treatment	Arm A, With Nitroglycerin (n = 60) No.	%	Arm B, Without Nitroglycerin (n = 60) No.	%	P
No. of chemotherapy courses delivered					
1	4	7	6	10	.38
2	5	8	7	23	
3	7	12	12	20	
4	44	73	35	47	
Total No. of courses	211		196		
Mean		3.52		3.27	
Median		4		3	
4 cycles without dose reduction	17	28	16	27	.84
4 cycles without delay in chemotherapy timing	16	27	20	33	.43
4 cycles without treatment modification	10	17	12	20	.64
Dose-intensity (% prescribed doses)					
Vinorelbine		79		78	.86
Cisplatin		76		74	.74

Table 4. Toxic Effects

Toxicity	Grade	Arm A, With Nitroglycerin (n = 60)	Arm B, Without Nitroglycerin (n = 60)	P
Leukopenia	2	21	22	.89
	3	15	17	
	4	22	20	
Neutropenia	2	23	16	.59
	3	17	14	
	4	18	20	
Anemia	2	32	28	.63
	3	5	7	
	4	1	2	
Thrombocytopenia	2	29	25	.55
	3	3	4	
	4	1	0	
Nausea or vomiting	2	21	19	.62*
	3	13	15	
	4	0	0	
Diarrhea	2	14	18	.92
	3	1	2	
	4	1	1	
Anorexia	2	33	31	.72
	3	15	19	
	4	2	3	
Cardiac toxic effects	2	2	2	> .99*
	3	1	1	
	4	0	0	
Renal dysfunction	2	5	3	> .99*
	3	0	0	
	4	0	0	
Neuropathy	2	2	3	.81*
	3	1	1	
	4	0	0	
Headache	2	3	1	> .99*
	3	0	0	
	4	0	0	
Hypotension	2	0	0	> .99*
	3	0	0	
	4	0	0	

*Comparison of grade 2 to 3 by Fisher's exact probability test.

that in arm B (42%; 25 of 60; odds ratio = 3.5; 95% CI, 1.7 to 7.6; $P < .001$). Conversely, the rate of no change in arm A (13%; eight of 60) was lower than that in arm B (35%; 21 of 60; odds ratio = 0.29; 95% CI, 0.1 to 0.7; $P = .006$). The rate of progressive disease in arm A did not differ from that in arm B (Table 5).

The use of nitroglycerin (RR = 4.3; 95% CI, 1.8 to 10.5; $P = .001$) and squamous cell carcinoma cell type (RR = 2.6; 95% CI, 1.0 to 6.5; $P = .049$) were associated positively with response rate in logistic regression analysis (Table 6).

TTP

The median follow-up period was 326 days (range, 32 to 1,380 days). Median TTP in arm A was 327 days (range, 32 to 1,151 days) compared with 185 days (range, 32 to 998 days) in arm B; use of nitroglycerin during chemotherapy (hazard ratio [HR] = 2.1; 95% CI, 1.3 to 3.2; $P = .002$) was associated with prolongation of TTP even after adjustment for age, sex, cancer cell type, and cancer staging in the Cox regression method. High performance status (PS 0; HR = 1.9; 95% CI, 1.4 to 2.7; $P < .001$) was also associated with prolongation of TTP. Kaplan-Meier analysis showed that progression-free probability in arm A was higher than that in arm B ($P = .006$; Fig 2).

Survival

We confirmed 100 deaths within the total of 120 patients by February 2005. In arm A, we confirmed that 46 of 60 patients had died and that 10 of 60 patients were alive at the end of the follow-up period, with four of 60 patients lost to follow-up. In arm B, we confirmed that 54 of 60 patients had died and that two of 60 patients were alive at the end of the follow-up period, with four of 60 patients lost to follow-up (Fig 1). Median survival time was 413 days (range, 32 to 1,380 days) in arm A, and 289 days (range, 56 to 1,117) in arm B. Treatment with nitroglycerin in arm A (HR = 2.5; 95% CI, 1.6 to 3.9; $P < .001$) was a significantly good prognostic factor compared with treatment without nitroglycerin even after adjustment for age, sex, cancer cell type, and cancer staging (Table 7). Kaplan-Meier analysis showed that survival probability in arm A was significantly higher than in arm B ($P < .001$; Fig 3).

Plasma VEGF Levels

In arm A patients, plasma VEGF levels after 3 days of treatment with nitroglycerin patches were significantly lower than levels before

Table 5. Response to Chemotherapy

Outcome	Arm A, With Nitroglycerin (n = 60)	Arm B, Without Nitroglycerin (n = 60)	P
Complete response	1	1	< .001
Partial response	42	24	
No change	8	21	
Progressive disease	9	14	

Table 6. Analysis of Risk Factors for Chemosensitivity Assessed by Multivariate Analysis

Characteristics	PR + CR (n = 68) No. of Patients	%	NC + PD (n = 52) No. of Patients	%	Logistic Regression Analysis Relative Risk	95% CI	P
Age, years							
≥ 60	46	61	30	39	1.28		.59
< 60	22	50	22	50		0.51 to 3.23	
Sex							
Male	59	51	46	49	0.47		.30
Female	9	60	6	40		0.11 to 1.96	
Performance status							
0	49	57	37	43	0.98		.96
1	19	56	15	44		0.49 to 1.96	
Cell type							
Squamous cell	39	75	13	25	2.56	1.00 to 6.54	.05
Adenocarcinoma	26	41	37	59	—		—
Large cell	3	60	2	40	0.63	0.07 to 5.29	.67
Staging							
IIIB	35	73	13	27	2.22		.10
IV	33	46	39	54		0.86 to 5.56	
Use of nitroglycerin							
Yes	43	72	17	28	4.31		.001
No	25	42	35	58		1.77 to 10.53	

Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

treatment (mean ± SE, 293 ± 50 *v* 205 ± 28 pg/mL; n = 6; $P = .03$). In arm B patients, plasma VEGF levels after 3 days of use of placebo patches did not differ from levels before use (286 ± 47 *v* 290 ± 48 pg/mL; n = 6; $P = .40$).

DISCUSSION

This randomized phase II trial was designed to evaluate the safety and efficacy of nitroglycerin combined with VC regimen in patients with stage IIIB/IV NSCLC. We demonstrated that treatment with nitroglycerin improved response rate, TTP, and survival time in patients with advanced NSCLC without the appearance of major adverse effects. The response rate in arm B (42%) is consistent with rates given in previous reports.[41-43] Furthermore, the response rate in arm A of our study (72%) was more than two times higher than that achieved in patients treated with VC alone in previous reports.[41,42] Median TTP and overall survival in arm A were longer than those in arm B (1.8 and 1.4 times, respectively). These findings suggest that use of nitroglycerin during chemotherapy may have beneficial effects on chemosensitivity in patients with NSCLC.

Although VC is a well-tolerated regimen,[41-43] we observed a high rate of severe neutropenia, especially on day 8 in the fourth course in both arm A (58%) and arm B (57%) in the present study. Therefore, we partially postponed the start timing of the fourth course of chemotherapy in both arms. A larger randomized trial is needed to study the toxicity profile in arm A.

Additional clinical benefit beyond four courses of VC therapy for patients with advanced NSCLC had not been reported at the start of our study. Smith et al[44] reported no evidence for additional clinical benefit by continuing mitomycin plus vinblastine and cisplatin beyond three courses in patients with NSCLC. Therefore, in our study, treatment for each arm was to be administered for a maximum of

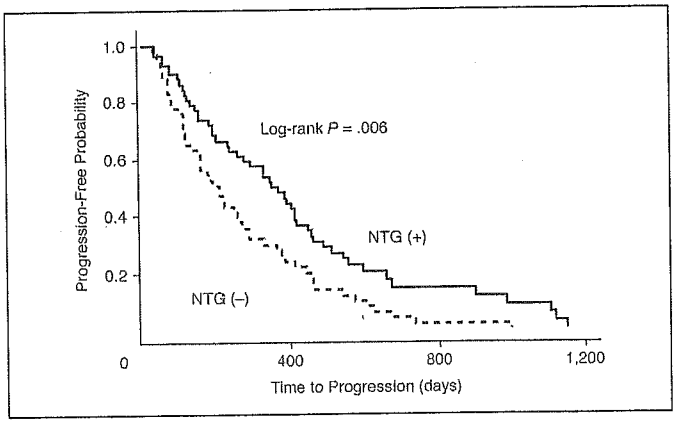

Fig 2. Disease progression free probability curves for patients with advanced non–small-cell lung cancer treated with nitroglycerin [NTG (+), (——)] and without nitroglycerin [NTG (–), (· · ·)] during chemotherapy. The *P* value was calculated by the log-rank test.

Table 7. Multivariate Analysis of Risk Factors Related to Survival

Variable	P	Risk Ratio	95% CI
Use of nitroglycerin combined with anticancer drugs, Yes* *v* No	< .001	2.5	1.6 to 3.9
PS 0* *v* PS 1	< .001	1.9	1.3 to 2.6

NOTE. All data were adjusted by age, sex, cancer staging, and smoking history (pack-year).
Abbreviation: PS, performance status.
*The group with better outcome.

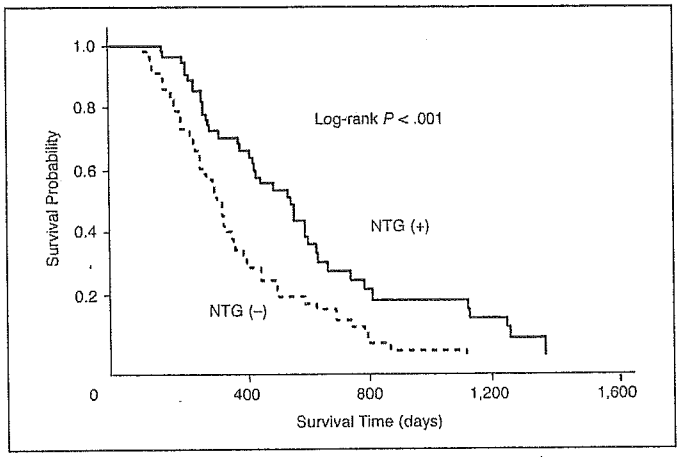

Fig 3. Survival probability curves for patients with advanced non–small-cell lung cancer treated with nitroglycerin [NTG (+), (——)] and without nitroglycerin [NTG (–), (· · ·)] during chemotherapy. The *P* [r] value was calculated by the log-rank test.

four courses. Additional study is needed to clarify whether there is additional clinical benefit beyond four courses of arm A treatment in patients with NSCLC.

In this study, there were higher rates of adenocarcinoma and of stage IV patients in arm B compared with arm A, although there were no statistically significant differences between the two arms in univariate analysis. Conversely, histological difference and staging of lung cancer were not associated significantly with response to chemotherapy in multivariate analysis with logistic regression analysis. These findings suggest that high rates of adenocarcinoma and stage IV patients in arm B might not contribute to the poorer response rate for that arm, although the possibility of contribution could not be ruled out.

The effects of NO donors on HIFs and tumor growth without the use of anticancer drugs are controversial.[17-20,26,27] However, NO-donating drugs such as nitroglycerin might reduce resistance to chemotherapy via improvement of hypoxic conditions,[10,13,16,21,45-51] reduced HIF-1 stabilization,[17-19] direct effects of NO on cancer cells,[22-24,52,53] increase in activated p53 protein,[20,25,54-56] and via an increase in drug delivery in tumor tissue. In this study, plasma levels of VEGF, an HIF-regulated protein,[39,57] after treatment with nitroglycerin for 3 days were lower than levels before nitroglycerin treatment. These findings suggest that reduced levels of plasma VEGF might be associated with mechanisms regarding an increase in response rate in patients treated with nitroglycerin. However, the number of patients whose plasma VEGF levels were measured was very small (n = 6 in each arm), and other HIF-regulated proteins including transforming growth factor alpha and thromobspondin-1[57] were not examined in this study. Therefore, it is still uncertain what mechanisms contribute to an increase in response rate in patients with NSCLC treated with nitroglycerin. Additional studies are needed to make clear the effects of nitroglycerin.

In summary, this is the first report demonstrating that combinational treatment with nitroglycerin during chemotherapy may enhance the response rate to VC, elongate the TTP, and improve overall survival in patients with advanced stage IIIB/IV NSCLC without major adverse effects in a randomized phase II trial. VC combined with nitroglycerin and VC alone are feasible and have acceptable toxicity profiles. To validate these provocative results, a prospective randomized phase III trial to evaluate nitroglycerin plus VC is underway in patients with stage IIIB/IV NSCLC.

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Anticoagulant Therapy for Idiopathic Pulmonary Fibrosis*

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Study objective: **To evaluate the effect of anticoagulant therapy on the survival of patients with idiopathic pulmonary fibrosis (IPF).**
Design: **Prospective study.**
Setting: **Five hospitals located in the Miyagi prefecture in Japan, including a university hospital, a Red Cross hospital, two public general hospitals, and a municipal hospital.**
Patients: **Fifty-six patients with IPF (mean age, 69.4 years; range, 47 to 89) admitted to the hospitals from April 2001 to April 2004.**
Interventions: **Patients were assigned to receive prednisolone alone or prednisolone plus anticoagulant therapy. The anticoagulants included oral warfarin in an outpatient setting and low-molecular-weight heparin for rehospitalized patients with severely progressive respiratory failure.**
Measurements and results: **There was no difference in baseline characteristics, including age, gender, clinical condition, pulmonary function, and plasma d-dimer level between the nonanticoagulant group and the anticoagulant group. The overall survival and hospitalization-free periods were assessed. There was a significant difference between survival curves of the nonanticoagulant group and the anticoagulant group, with a 2.9 hazard ratio ($p = 0.04$, Cox regression model). There was no significant difference in the probability of a hospitalization-free period between groups. The major cause of clinical deterioration was acute exacerbation during follow-up in the present study. Therefore, the mortality and plasma d-dimer levels in patients with an acute exacerbation were also assessed. The mortality associated with acute exacerbations of IPF in the anticoagulant group was significantly reduced compared to that in the nonanticoagulant group (18% vs 71%, respectively; $p = 0.008$, Fisher Exact Test). Furthermore, the plasma d-dimer levels in patients who died were significantly higher than those in survivors during acute exacerbation of IPF (3.3 ± 2.3 μg/mL vs 0.9 ± 0.7 μg/mL, $p < 0.0001$). Histologic analysis performed in three patients who died due to an exacerbation of IPF in the nonanticoagulant group demonstrated the features of usual interstitial pneumonia and acute lung injury.**
Conclusions: **Our data suggested that plasma d-dimer levels are associated with mortality in patients with an acute exacerbation of IPF, and that anticoagulant therapy has a beneficial effect on survival in patients with IPF.** ***(CHEST 2005; 128:1475–1482)***

Key words: acute exacerbation; anticoagulant therapy; idiopathic pulmonary fibrosis; low-molecular-weight heparin; prognosis; survival; warfarin

Abbreviations: %FVC = percentage of predicted FVC; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, diffuse interstitial pulmonary disease associated with a histologic appearance of usual interstitial pneumonia. IPF has a worse prognosis, and the median survival is 4 to 5 years after symptoms of cough or breathlessness develop.[1] IPF is characterized by progressive injury, inflammation, and fibrosis of the lung parenchyma.[1] The prognosis of acute

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exacerbations of IPF was reported to be very poor.[2–5] There is no effective therapy with proven and unequivocal benefits currently available, and the nature and appropriate therapy for this condition are still to be established.

Fibrotic lung diseases are accompanied by inflammation and vascular injury.[6–8] Abundant neointimal tissue factor, a maximal prothrombotic stimulus, is exposed to circulating blood following endothelial disruption, thereby triggering rapid coagulation. Thus, thrombosis in the pulmonary vasculature might exist especially where alveolitis and/or fibrotic processes of the lung are present. In fact, although pulmonary embolism is a documented cause of death in IPF patients,[9] few reports focus on the role of the coagulation system in IPF. The aims of the present study were to evaluate whether a coagulation disorder occurs in IPF patients, and whether the administration of anticoagulant agents has a beneficial effect on the survival of patients with IPF.

Materials and Methods

Patients

We conducted a prospective study of 56 patients with IPF who were admitted to five hospitals located in the Miyagi prefecture in Japan from April 2001 to April 2004. The hospitals were a university hospital, a Red Cross hospital, two public general hospitals, and a municipal hospital. Before enrollment in this study, all patients had received a diagnosis of IPF and had demonstrated progressive deterioration of IPF in varying degrees, despite conventional therapy without prednisolone. The mean age at the time of hospital admission was 69.4 years (range, 47 to 89). The diagnosis of IPF was determined previously by either histologic evaluation of open-lung biopsy or transbronchial lung biopsy specimens, or radiologic evaluation using high-resolution CT (HRCT), or both. Histologic evidence demonstrated the characteristics of usual interstitial pneumonia and showed the various stages of interstitial lung disease including alveolitis, fibrosis, honeycombing, and a patchy reticular pattern that was predominantly evident in the basal region of the periphery of the lung field and was associated with traction bronchiectasis. HRCT-based diagnosis was performed by two radiologists who did not know the purpose of the present study. The typical HRCT appearance demonstrated honeycombing, intralobular reticulations, and traction bronchiectasis with or without ground-glass opacification.[10–12] Nonspecific interstitial pneumonia was excluded based on histologic findings or HRCT appearance. Patients were excluded if they had clinical or serologic evidence of collagen vascular disease, a history of exposure to known fibrogenic agents, active infection, malignancy, hemoptysis, hypersensitive pneumonitis, GI bleeding, or ARDS. Patients were also excluded if they had obvious signs of preexisting pulmonary embolism, pulmonary hypertension due to pulmonary thromboembolism, or phlebitis by color Doppler ultrasonography or enhanced CT. All patients were nonsmokers. Pulmonary function tests (percentage of predicted FVC [%FVC] and carbon monoxide diffusing capacity) and blood gas analysis (Pa_{O_2}) were performed on enrollment in this study.

Intervention

To evaluate the effect of anticoagulant therapy on the survival of patients with IPF, participants were randomly assigned to receive oral prednisolone alone (nonanticoagulant group) or oral prednisolone plus oral warfarin (anticoagulant group). The oral prednisolone therapy in both groups was performed initially at a dosage of 0.5 to 1.0 mg/kg/d for 4 weeks, with subsequent tapering of the dose to 10 to 20 mg/d over a 1-month period. Warfarin was used for patients in the anticoagulant group at the dose required to keep the values of the international normalized ratio between 2.0 and 3.0. All patients were informed of the protocol of this study on enrollment. We used random-number tables for simple randomization. As a result of random allocation, there were 33 patients in the nonanticoagulant group and 31 patients in the anticoagulant group. Among the 31 patients in the anticoagulant group, 6 patients declined participation because they were afraid of side effects and disliked the extra blood sampling required for monitoring the international normalized ratio. One patient stopped the study due to purpura. One patient dropped out because he moved to another prefecture. Our final enrolled cohort included 33 patients in the nonanticoagulant group and 23 patients in the anticoagulant group.

During follow-up, approximately 60% of all patients were rehospitalized due to severely progressive respiratory failure secondary to various causes including acute exacerbation of IPF, bacterial pneumonia, heart failure, or sepsis. During the period of hospitalization for these crises, patients in the anticoagulant group received IV low-molecular-weight heparin, dalteparin sodium instead of oral warfarin, at a dose of 75 IU/kg/d for 1 to 2 weeks. No serious complications, such as bleeding, were observed with the anticoagulant agents. Steroid therapy was stopped for patients readmitted with obvious bacterial infection or heart failure. Conversely, patients readmitted with an acute exacerbation of IPF were treated with high doses of methylprednisolone (500 to 1,000 mg/d) for 3 days. All patients in both groups who were readmitted received oxygen therapy and antibiotic treatment. Acute exacerbations were defined as previously described with a slight modification[2]: (1) exacerbation of dyspnea within a few weeks; (2) newly developing diffuse pulmonary infiltrates on chest radiographs or HRCT; (3) deterioration of hypoxemia (Pa_{O_2}/fraction of inspired oxygen < 300); and (4) absence of infectious pneumonia, heart failure, and sepsis.

The primary end points of this study were overall survival time to death and hospitalization-free period. Survival time to death was calculated from the initial visit until death or censoring. The hospitalization-free period was also calculated from initial visit until the second hospitalization due to severely progressive respiratory failure or censoring.

Plasma D-dimer

D-dimer is a final product of cross-linked fibrin degradation and is released into the circulation during the process of endogenous fibrinolysis. D-dimer has been reported to be elevated in acute myocardial infarction,[13] unstable angina,[14] and deep venous thrombosis,[15] as well as in patients with suspected pulmonary embolism.[16] Furthermore, the procedure for d-dimer is simple, inexpensive, and noninvasive, compared to angiography or scintigraphic examination. Therefore, d-dimer and high-molecular-weight fibrin degradation products are thought to be useful markers of abnormal coagulation balance.[17] However, to our knowledge, there is no report on the plasma d-dimer level in patients with acute exacerbation of IPF. The d-dimer assay was performed in all participants at entry to this study. The plasma d-dimer was also measured in patients with an acute exacerbation

of IPF (21 patients in the nonanticoagulant group and 11 patients in the anticoagulant group) on the first and 14th days following readmission to the hospital.

For the measurement of plasma d-dimer levels, blood samples were collected by clean venous puncture into tubes containing 3.8% trisodium citrate (9:1, volume/volume). Platelet-poor plasma was obtained by centrifuging at 3,000g for 15 min. Plasma d-dimer levels were measured using an enzyme immunosorbent assay (Boehringer; Mannheim, Germany).[18] The normal level for plasma d-dimer in our laboratory is < 0.5 μg/mL.

Statistical Analysis

Comparisons of baseline characteristics between the nonanticoagulant group and the anticoagulant group were tested by an unpaired *t* test and χ^2 test. Values are reported as mean ± SD. Significance was accepted at $p < 0.05$. Survival time to death was calculated from the initial visit until death or censoring. Patients were censored if they were still alive at the last contact. Survival estimates were computed using standard Kaplan-Meier estimates with the log-rank test for the p value of survival curves between patients with and without anticoagulant therapy. Cox regression analysis was also performed to assess the relative risk of survival curves between the anticoagulant group and the nonanticoagulant group, which was adjusted for age and baseline %FVC. Statistical software (StatView version 5.0; SAS Institute; Cary, NC) was used for analysis.

RESULTS

Patient Characteristics

There was no difference in baseline characteristics, including age at enrollment, gender, clinical condition, pulmonary function, and plasma level of d-dimer, between the nonanticoagulant group and the anticoagulant group (Table 1). The overall mean age was 69.4 years. There were 31 men and 25 women. The overall %FVC was 70%. All participants were nonsmokers. The mean plasma d-dimer level was increased at the time of the initial visit (2.02 ± 1.3 μg/mL).

Survival to Death

Twenty of the 33 patients in the nonanticoagulation group died during follow-up (median, 399 days; range, 35 to 1,106). Five of the 23 patients in the anticoagulant group died during follow-up (median, 347 days; range, 55 to 1,106) [Table 2]. The 1-year survival rates for the nonanticoagulant group and the anticoagulant group were 58% and 87%, respectively. The 3-year survival rates for the nonanticoagulant group and the anticoagulant group were 35% and 63%, respectively. There was a significant difference between the survival curves of the two groups (Fig 1; $p = 0.049$, log-rank test). According to the Cox regression model, the hazard ratio, which was adjusted for age and baseline %FVC, was 2.9 (95% confidence interval, 1.0 to 8.0; $p = 0.04$) for death in the nonanticoagulant group compared to the anticoagulant group (Fig 1).

Rehospitalization and Hospitalization-Free Period

Twenty-two patients in the nonanticoagulant group were rehospitalized with acute respiratory failure during follow-up. Since some patients were rehospitalized several times, the total number of rehospitalizations in this group was 29. Thirteen patients in the anticoagulant group were hospitalized with a total of 15 hospitalizations (Table 2). The hospitalization-free period was calculated from the initial visit until the second hospitalization. The

Table 1—*Baseline Characteristics of the Patients**

Characteristics	Nonanticoagulant Group (n = 33)	Anticoagulant Group (n = 23)	p Value
Age, yr	68.1 ± 9.7	71.3 ± 10.6	0.26†
Male/female gender	17/16	14/9	0.67‡
Method of diagnosis			
Open-lung biopsy	5	4	> 0.9‡
Transbronchial biopsy	12	8	> 0.9‡
HRCT	33	23	> 0.9‡
Clinical condition			
Hugh-Jones score	3 ± 1	3.3 ± 0.5	0.34†
Need for supplemental oxygen	11	11	0.42‡
Pulmonary function			
%FVC	71 ± 17	69 ± 13	0.76†
PaO_2	73 ± 9	70 ± 10	0.17†
DLCO, % predicted	63 ± 14	59 ± 15	0.49†
Plasma d-dimer, mg/mL	1.9 ± 1.3	2.1 ± 1.6	0.73†

*Data are presented as mean ± SD or No. DLCO = diffusion capacity of the lung for carbon monoxide.
†Unpaired *t* test.
‡χ^2 test.

Table 2—*Clinical Outcome During Follow-up**

Variables	Nonanticoagulant Group (n = 33)	Anticoagulant Group (n = 23)	p Value
Rehospitalization, No. of patients	22	13	0.6*
Once	17	11	
Twice	3	2	
Three times	2	0	
Causes of rehospitalization, total No. of hospitalizations	29	15	
Acute exacerbation	21	11	
Pneumonia	6	2	
Heart failure	1	1	
Sepsis	1	1	
Death, No. of patients	20	5	0.006†
Causes of death, total No. of patients	20	5	
Acute exacerbation	15	2	
Pneumonia	3	1	
Heart failure	1	1	
Sepsis	1	1	

*χ^2 test.
†Fisher Exact Test.

probability of a 1-year period without hospitalization was 39% for the nonanticoagulant group and 74% for the anticoagulant group, but this was not statistically significant (p = 0.3, log-rank test) [Fig 2].

Acute Exacerbation of IPF and Plasma D-dimer Level

At readmission to the hospital with progressive respiratory failure, all patients underwent ultrasonic cardiography, HRCT scanning with enhancement, blood biochemical analysis, and blood and sputum microbiological analysis together with a physical examination. The causes of readmission to the hospital included acute exacerbation of IPF, pneumonia, heart failure, and sepsis (Table 2). There were no cases with obvious pulmonary thromboembolism or deep venous thrombosis. Acute exacerbation of IPF was the most frequent cause of readmission to the hospital in both the nonanticoagulant group and the anticoagulant group (72% and 73%, respectively). However, the mortality from acute exacerbation of IPF in the anticoagulant group was significantly reduced compared to that in the nonanticoagulant group (15 deaths in 21 acute exacer-

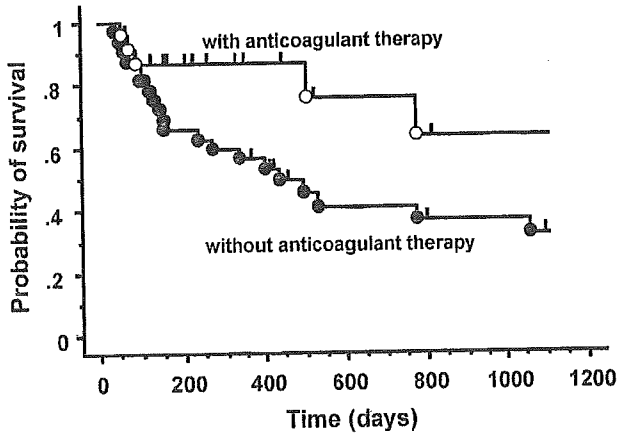

FIGURE 1. Kaplan-Meier survival estimate with censoring (⊥) between the nonanticoagulant group and the anticoagulant group in regard to overall survival. Open circles indicate the survival curve in the anticoagulant group. Closed circles indicate the survival curve in the nonanticoagulant group. There was a statistical significance between survival curves of the anticoagulant group and the nonanticoagulant group (p = 0.049, log-rank test). According to the Cox regression model, the hazard ratio for death was 2.9 in the nonanticoagulant group compared to the anticoagulant group (adjusted for age and baseline %FVC; 95% confidence interval, 1.0 to 8.0; p = 0.04).

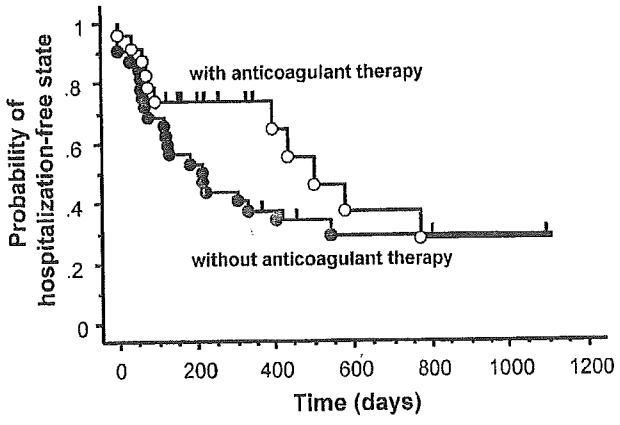

FIGURE 2. Kaplan-Meier estimate with censoring (⊥) between the nonanticoagulant group and the anticoagulant group in regard to hospitalization-free period. Open circles indicate the survival curve in the anticoagulant group. Closed circles indicate the survival curve in the nonanticoagulant group. There was no statistical significance of probability of hospitalization-free period between the anticoagulant group and the nonanticoagulant group (p = 0.3, log-rank test).

bations vs 2 deaths in 11 acute exacerbations, respectively; p = 0.008, Fisher Exact Test; Table 2).

The plasma d-dimer levels in the anticoagulant group were reduced by oral warfarin administration before readmission to hospital (1.1 ± 1.2 μg/mL). However, the plasma d-dimer levels on the first day of readmission to hospital with acute exacerbation were slightly elevated in both groups (2.2 ± 1.1 μg/mL in the nonanticoagulant group vs 2.1 ± 1.0 μg/mL in the anticoagulant group). The plasma d-dimer level in the anticoagulant group with acute exacerbation was significantly reduced by IV administration of dalteparin sodium (2.1 ± 1.0 μg/mL on day 1, vs 0.8 ± 1.0 μg/mL on day 14 (p = 0.01, paired *t* test; Fig 3). Conversely, no significant difference between the plasma d-dimer levels on day 1 and day 14 following readmission to the hospital was evident in the nonanticoagulant group with acute exacerbation. The changes in plasma d-dimer levels of the patients before and during readmission to hospital with acute exacerbation are summarized in Table 3. Finally, 17 of 32 patients with an acute exacerbation of IPF died during hospitalization (15 of 21 patients in the nonanticoagulant group and 2 of 11 patients in the anticoagulant group; Fig 3). The plasma d-dimer level on day 14 in the deceased patients was significantly higher than that in the survivors of an acute exacerbation of IPF (3.3 ± 2.3 μg/mL vs 0.9 ± 0.7 μg/mL, p < 0.0001).

Pathology Findings

We performed postmortem examinations in three patients with an exacerbation of IPF in the nonanticoagulant group. All exhibited similar histologic characteristics with the usual interstitial pneumonia and superimposed features of acute lung injury (Fig 4, *top left*, *A*, and *top right*, *B*). There was a honeycomb appearance in the subpleural zone and diffuse consolidation of lung parenchyma by septal fibrosis. There was also a diffuse and exudative alveolar damage with varying degrees of hyaline membranes. Furthermore, a few small clots were detected in the alveolar capillary bed in 1 patient (Fig 4, *bottom left*, *C*), and there was evidence of fibrin deposition in the alveolar space of another patient; stained red with Elastica-Masson staining (Fig 4, *bottom right*, *D*). However, no evidence of massive pulmonary embolism was found in these samples.

Discussion

In this study, we found a beneficial effect of combined anticoagulant and prednisolone therapy on the survival of IPF patients. Corticosteroids are the mainstay of therapy in IPF patients. However, medication with corticosteroid alone resulted in a poor prognosis, with a 3-year survival of 35% in the

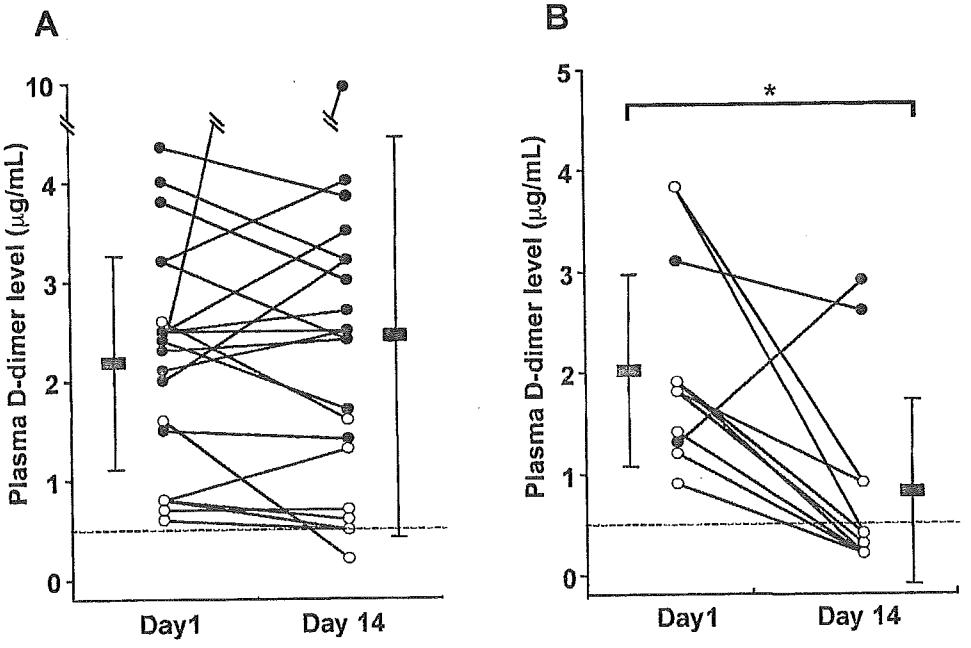

Figure 3. Comparisons of plasma d-dimer levels on day 1 and day 14 during hospitalization due to acute exacerbation of IPF in the nonanticoagulant group (*left*, *A*) and the anticoagulant group (*right*, *B*). Open circles indicate the values from survivors with acute exacerbation of IPF. Closed circles indicate those from patients who died during hospitalization. The bold black bars indicate the mean values of groups; *p = 0.01, paired *t* test. The dashed line indicates the upper limit of the plasma d-dimer level (< 0.5 μg/mL).

Table 3—*Changes in Plasma D-dimer Levels**

Variables	Nonanticoagulant Group	Anticoagulant Group	p Value†
Before rehospitalization, No. of patients	33	23	
Baseline values	1.9 ± 1.3	2.1 ± 1.6	0.7
After enrollment before rehospitalization	2.0 ± 1.5	1.1 ± 1.2	0.04
During acute exacerbation, No. of hospitalizations‡	21	11	
On day 1 of rehospitalization	2.2 ± 1.1	2.1 ± 1.0	0.7
On day 14 of rehospitalization	2.5 ± 2.1	0.8 ± 1.0	0.02

*Data are presented as mean ± SD micrograms per milliliter unless otherwise indicated. The normal level for plasma d-dimer in our laboratory is < 0.5 μg/ mL.
†Unpaired t test.
‡Rehospitalizations due to pneumonia, heart failure, and sepsis were excluded.

present study as previously reported.[19] In contrast, combined therapy with combined anticoagulant and prednisolone therapy gave a better prognosis, with a 3-year survival of 63% in the present study. Although corticosteroids exert a potent anti-inflammatory effect, they may induce a hypofibrinolytic state.[20] It is possible that anticoagulation cancels out the adverse effect of corticosteroid on the intravascular coagulation balance. We did not have a patient group treated with anticoagulation alone, and it is therefore unclear if the improved prognosis resulted from the effects of anticoagulation alone or the combined

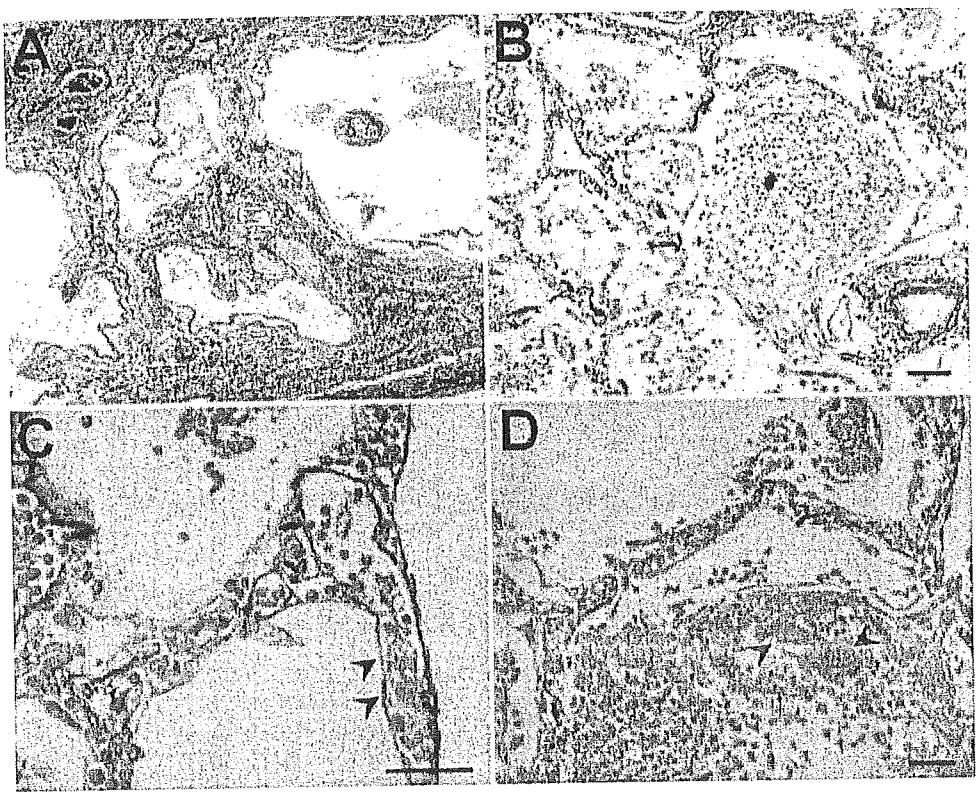

FIGURE 4. Histopathologic analysis of lung tissue derived from patients who died due to exacerbation of IPF in the nonanticoagulant group. All samples were stained with Elastica-Masson staining. Each bar in the panel indicates 50 μm. *Top left, A*: fibrosing stage of IPF, with marked fibrosis and dilatation of residual airspaces with glandular metaplasia and a honeycomb appearance. *Top right, B*: acute exacerbation of IPF, revealing histologic features of diffuse alveolar damage including edematous thickening and hyperemia of the alveolar wall with marked swelling of reactive type II pneumocytes. Note the extensive hyaline membrane formation and focal intra-alveolar organization with an active mesenchymal cell reaction (fibroblastic foci). *Bottom left, C*: an area of the alveolar capillary bed with large magnification from one patient who died due to acute exacerbation of IPF. A small clot was detected in the dilated capillary (arrows). *Bottom right, D*: fibrin deposition in an alveolar space from another patient. The fibrin deposition was stained red with Elastica-Masson staining (arrows).