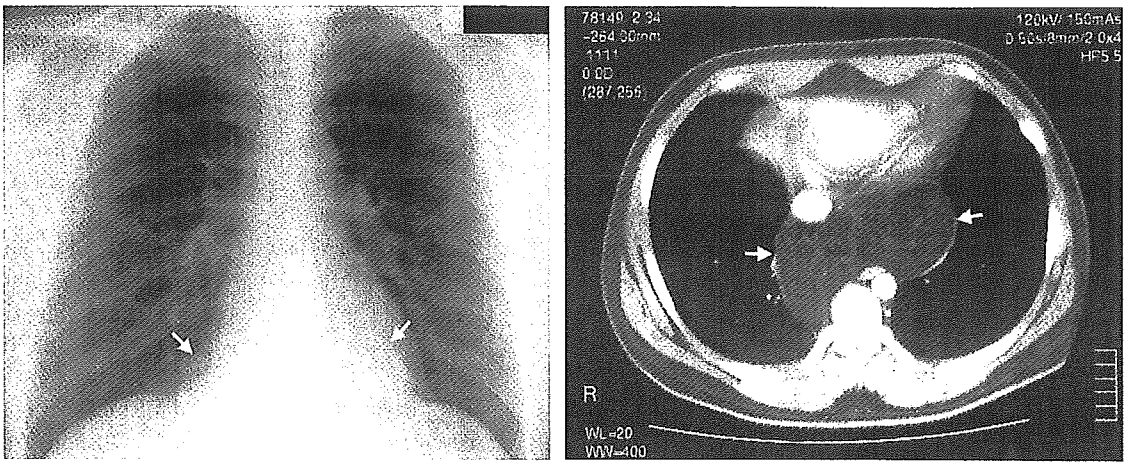
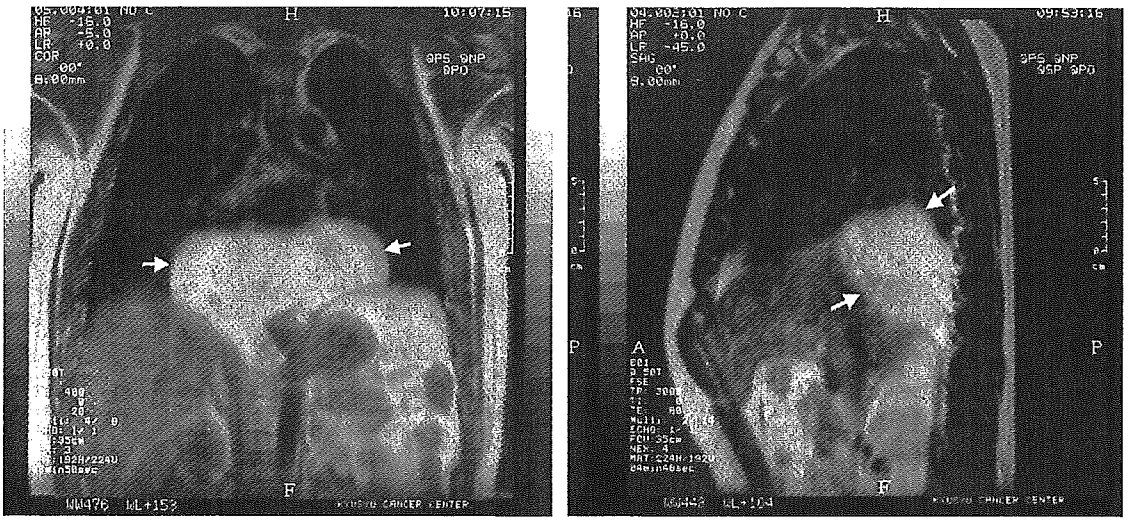


A B

Fig. 1.
A: Postero-anterior view of a chest X-ray demonstrates a large retrocardiac mass (arrows).
B: A CT scan (axial section) demonstrates a large retrocardiac fatty mass (arrows).



A B

Fig. 2. Coronal (A) and sagittal (B) sections of T1-weighted MRI clearly depict a fatty mass on both sides of the diaphragm (arrows).

congenital defects of the diaphragm, such as Morgagni or Bochdalek defects. However, there have only been eight reports on omental herniation through the esophageal hiatus in the Japanese and English literatures within last three decades.[1-8] Omental herniation has previously either been misdiagnosed as intrathoracic lipomatous tumor or has been resected without a conclusive diagnosis.[1] CT and MRI are very useful modalities for establishing a differential diagnosis preoperatively.[4,5] However, a correct diagnosis of omental herniation requires evidence of omental fat accompanied with omental vesseles passing through the esophageal hiatus. In this case, vascular structures were recognized on the CT scan. However, it is difficult to distinguish these components from areas of neovascularity due to malignant formation. Kubota et al. performed celiac arteriography to rule out the possibility of a lipomatous tumor.[8] Since angiography is an invasive diagnostic procedure, they also recommend dynamic MRI or reconstructed 3 dimension (3D) MR angiography as alternatives to angiography.

Eliska suggested that the phreno-esophageal membrane can act as one of the main mechanisms of competence in the cardio-esophageal junction, and thus preventing reflux and hiatal hernia.[10] This membrane has two limbs, one which passes through the esophageal hiatus, and then attaches itself to the esophagus in the chest, while the other limb extends downward and attaches itself to the esophagus in the abdomen. The membrane is normally rich in elastic fibers, but in people over 50 years of age, the amount of elastic tissue tends to decrease and the esophagus becomes much more mobile within the hiatus. In obese patients, the omentum may also be more prominent than usual, thus predisposing it to herniation without any significant gastroesophageal hernia. It is generally assumed that the major contributing factors leading to an omental herniation through the esophageal hiatus include aging and obesity. Therefore, previous reports about omental herniation all described either middle-aged or elderly patients.[1-8] This is the first report of intrathoracic omental herniation through the esophageal hiatus in a patient still in his twenties. The weakness of the phreno-esophageal membrane was not recognized based on an intraoperative view. In addition to obesity, these findings indicate the possibility that some congenital anomaly may thus have existed in the esophageal hiatus in our case and an omental mass thereafter formed as the patient became older.

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Clinical Studies

UFT plus gemcitabine combination chemotherapy in patients with advanced non-small-cell lung cancer: a multi-institutional phase II trial

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A multi-institutional phase II trial was conducted to evaluate the efficacy and toxicity of combination chemotherapy consisting of gemcitabine and UFT, which is composed of tegafur and uracil, for non-small-cell lung cancer (NSCLC) patients. Patients with advanced NSCLC received an oral administration of UFT (tegafur 200 mg m^{-2}) b.i.d. from days 1 to 14 and intravenous injection of gemcitabine 900 mg m^{-2} on days 8 and 15. This treatment was repeated every 4 weeks. A total of 44 patients were enrolled into this trial. The median age of all patients was 74 years, with 23 patients younger than 75 years and 21 patients with 75 years of age or older. A total of 18 patients (41%) achieved a partial response. The median survival time was 13.2 months and the 1-year survival rate was 59%. The most common grade 3–4 toxicity was neutropenia (57%). The frequency of grade 3 nonhaematologic toxicities was less than 5%. In addition, no significant difference in the response, survival or toxicities was observed between the patients younger than and those older than 75 years of age. This combination chemotherapy demonstrated a promising effectiveness and acceptable toxicity in patients with advanced NSCLC, even in patients older than 75 years.
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UFT is an oral anticancer agent composed of tegafur and uracil at a 1:4 fixed molar ratio (Fujii *et al*, 1979). Although the clinical effectiveness of the single agent against advanced non-small-cell lung cancer (NSCLC) has not been evaluated in adequate sample size (Keicho *et al*, 1986), a recent randomised phase III trial in 984 patients with completely resected stage I adenocarcinoma demonstrated that postoperative adjuvant chemotherapy with UFT significantly prolonged the survival of patients in comparison to observation alone (Kato *et al*, 2004). The combination chemotherapy of UFT plus cisplatin has also been reported to be an effective treatment for advanced NCSLC. The combination chemotherapy consisting of a daily administration of UFT for 2 or 3 weeks and a bolus injection of cisplatin at the mid-cycle of the administration of UFT yields a response rate of 29–38%, and a median survival time of 10–13 months (Ichinose *et al*, 1995, 2000; Saito *et al*, 2001).

Gemcitabine is an active anticancer agent for the treatment of NSCLC. The objective response rates of patients with advanced NCSLC treated with gemcitabine alone and the combination chemotherapy of platinum plus gemcitabine range from 20 to 26% and from 25 to 61%, respectively (Harper, 2003). A median survival time of 8–16 months in patients treated with the combination chemotherapy has been reported (Harper, 2003).

Both 5-FU generated from tegafur in UFT and gemcitabine are antimetabolites but inhibit DNA synthesis via a different pathway. The main mechanism of inhibiting DNA synthesis by 5-FU is due to 5-FU-derived fluorodeoxy monophosphate binding to thymidylate synthase (Madajewicz *et al*, 1984). The incorporation of gemcitabine triphosphate, which is generated from the phosphorylation of gemcitabine by deoxycytidine kinase, into DNA is most likely the major mechanism by which gemcitabine exerts its cytotoxic action (Huang *et al*, 1991). Such different antitumour mechanisms suggest a potential synergism between 5-FU and gemcitabine. This potential synergism has been indeed observed in *in vitro* studies using various cancer cell lines (Schulz *et al*, 1998; Peters *et al*, 2000).

In our prior phase I trial, the combination chemotherapy of UFT plus gemcitabine was found to be feasible (Seto *et al*, 2002). The most appropriate schedule and dosing was 200 mg m^{-2} of UFT b.i.d for 14 consecutive days with 900 mg m^{-2} gemcitabine on days 8 and 15. The main toxicity was haematologic. The overall response rate was 33%, while the rate was 45% in the 13 patients without any prior chemotherapy. With these backgrounds, we conducted a phase II trial of combination chemotherapy using

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UFT plus gemcitabine. In the present multi-institutional phase II trial, we found the proportion of elderly, especially patients older than 75 years of age, to be high. Therefore, the results of all patients in the phase II trial and the differences between patients younger than 75 years and those 75 years of age or older were evaluated.

MATERIALS AND METHODS

Patient eligibility

The patients were eligible for this phase II trial if they had been either cytologically or histologically confirmed to have NSCLC; stage IIIB without any indications for radiotherapy or stage IV; measurable disease; no prior chemotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2; a projected life expectancy of at least 3 months. Other eligibility criteria regarding organ functions were as follows: a leucocyte count of 4000–12 000 l^{-1}; platelet count of 100 000 μl^{-1} or greater; haemoglobin level of 9 g dl^{-1} or greater; a serum bilirubin level less than 1.5 mg dl^{-1}; serum aspartate aminotransferase and alanine aminotransferase levels of twice the upper limit or less; a serum creatinine level of 1.5 mg dl^{-1} or less. For staging, all patients underwent a computed tomography (CT) scan of the thorax, including the upper abdomen, and either brain CT or magnetic resonance images of the brain, and a radioisotopic bone scan were performed for almost all patients.

Any patients who were pregnant or had concomitant serious diseases, a concomitant malignancy, pleural effusion necessitating treatment or symptomatic cerebral involvement were excluded from the study. However, patients whose malignant pleural effusion was controlled by intrapleural hypotonic cisplatin treatment (Ichinose *et al*, 2003) were eligible. Written informed consent was required from all patients and the protocol was approved by the institutional ethics committee of each of the participating institutions. On entrance to the study, the eligibility of patients was checked via facsimile by the central administration office of the Kyushu Yamaguchi Thoracic Oncology Group (Fukuoka).

Treatment schedule

UFT (tegafur 400 mg m^{-2} day^{-1}) in the form of a 100-mg capsule (100 mg of tegafur plus 224 mg of uracil) was given orally in two separate doses, before meals, from days 1 to 14. The dose was rounded up or down to the nearest 100 mg. Most patients received UFT three capsules (tegafur 300 mg and uracil 672 mg) b.i.d. Gemcitabine (900 mg m^{-2}) was dissolved in 20 ml of physical saline and then diluted further with physical saline or 5% glucose to a volume of 250 ml. The gemcitabine solution was administered by intravenous drip infusion over 30 min on days 8 and 15. On the day gemcitabine was administered, a complete blood count was performed and the drug was administered only when the leucocyte count was 2000 μl^{-1} or higher and the platelet count was 70 000 or higher μl^{-1}. If these requirements were not met, then drug administration was postponed for a maximum of 4 days. The treatment regimen was repeated every 4 weeks and at least two cycles were administered unless disease progression or an unacceptable toxicity occurred. A leucocyte count of 3000 μl^{-1} or greater and the entry eligibility criteria regarding organ functions had to be satisfied to start the next cycle. The doses of gemcitabine were reduced to 800 mg m^{-2} either when grade 4 haematologic toxicities occurred or when the administration of gemcitabine on day 15 was skipped in a prior cycle. The doses were increased to 1000 mg m^{-2} if both nadirs of the leucocyte and platelet counts were more than 3000 and 100 000 μl^{-1}, respectively, in a prior cycle.

Evaluation of response and toxicity

All eligible patients who received any part of the treatment were considered assessable for response and toxicity. The complete blood count, and blood chemistry studies were repeated weekly. The response was assessed based on the chest X-ray or CT scan findings that initially had been used to define tumour extent. The response was evaluated according to the criteria of the World Health Organization (Miller *et al*, 1981). A central radiologic review was performed to determine the eligibility of patients and the response of treatment. Any adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0.

Statistical analysis

The primary end point of this study was to determine the tumour response rate produced with this treatment protocol. Based on the assumption that a response rate of higher than 40% would warrant a further investigation of this combination chemotherapy, and that a rate of below 20% would make such an investigation unnecessary, a sample size of 36 patients was required with an alpha error of 0.05 and a beta error of 0.2. Therefore, the accrual of 40 patients was planned for a 2-year period since several ineligible patients might be identified in the course of the study.

The overall survival of the eligible patients was defined as the time from the start of the treatment until death from any cause and it was estimated by the Kaplan–Meier method. Differences between the proportions were evaluated by the chi-square test. The data were considered to be significant when the *P*-value was 0.05 or less.

RESULTS

Patient characteristics

From July 2000 to September 2002, 44 patients were entered into this phase II trial. Since no upper age limit for the eligibility criteria was established, in contrast to other Japanese trials, many elderly patients were included in this trial. The patient characteristics classified by an age of less than 75 years of age or 75 years of age and older are shown in Table 1. There were no statistically significant differences in the proportions regarding gender, performance status, stage, histology or previous treatment between the two (<75 *vs* $\geqslant 75$ years) groups. There were 33 patients who were 70 years of age or older.

Treatment delivery

The median number of treatment cycles for all patients was three as shown in Table 2. In all, 39 (89%) patients received at least two cycles of the treatment. The reasons for terminating the chemotherapy before the second treatment cycle were adverse events in three patients, a progression of dementia in one and patient refusal in one. Although the proportions of the cycles administered between the two-age groups showed no significant difference, 10 (48%) patients in the older age group received five or more cycles of the treatment.

The administration of gemcitabine on day 15 was skipped in 10 (5%) of a total of 196 cycles. A dose decrease to 800 mg m^{-2} and the increase to 1000 mg m^{-2} were reported in four and five patients, respectively.

Adverse events

The main adverse events were haematologic toxicities as shown in Table 3. Grade 3 and 4 neutropenia was reported in 57% of the patients and grade 4 in 20%, while no grade 4 anemia or

Table 1 Patient characteristics

	<75 years (n=23)	≥75 years (n=21)	Total (n=44)
Age			
Median (range)	70 (58–74)	78 (75–89)	74 (58–89)
Gender			
Male/female	7/16	11/10	18/26
Performance status (ECOG)			
0/1/2	8/13/2	8/13/0	16/26/2
Stage			
III/IV	5/18	7/14	12/32
Histology			
Adenoca/others	17/6	15/6	32/12
Previous treatment			
None	11	11	22
HPT[a]	6	8	14
Operation	5	2	7
Radiotherapy	1	0	1

[a]Hypotonic cisplatin treatment. ECOG = Eastern Cooperative Oncology Group.

Table 2 Treatment delivery

Cycle of treatment	<75 years (n=23)	≥75 years (n=21)	Total (n=44)
1	23 (100%)	21(100%)	44 (100%)
2	21 (91%)	18 (86%)	39 (89%)
3	12 (52%)	14 (67%)	26 (59%)
4	9 (39%)	11 (52%)	20 (45%)
≥5	6 (26%)	10 (48%)	16 (36%)
No. of cycles			
Median	3	4	3
Range	1–18	1–16	1–18

thrombocytopenia was observed. The frequency of grade 3 and 4 haematologic toxicities was 57% in the younger-age group and 62% in the older-age group. The frequency of grade 3 or greater nonhaematologic toxicities was 5% or less. No grade 4 nonhaematologic toxicity was observed.

Response

Among the 44 patients, 18 patients showed a partial response (41%; 95% confidence interval, 26–55%). There were 24 patients (55%) with no change and two patients (5%) with progressive disease. There were no differences in the response rate according to age (<75 *vs* ≥75 years, 44 *vs* 38%), gender (male *vs* female, 46 *vs* 33%), stage (III *vs* IV, 42 *vs* 41%) and histology (adenocarcinoma *vs* others, 44 *vs* 33%). Median duration of response was 6.9 months.

Survival

The overall median follow-up time for all patients was 38 months (range from 23 to 50 months). As shown in Figure 1, the median survival time of all 44 patients was 13.2 months, and the survival rates at 1 and 2 years were 59% (95% confidence interval, 45–74%) and 34% (95% confidence interval, 20–48%), respectively. There were no statistically significant differences in survival between the patients under 75 and those over 75 years ($P=0.4948$). The median survival time was 13.2 and 13.3 months, respectively.

Table 3 Haematologic and nonhaematologic toxicities (n=44)

	Grade				
Toxicity	**1**	**2**	**3**	**4**	**Frequency of Grade 3 or 4 (%)**
Leukopenia	4	19	13	1	32
Neutropenia	5	8	16	9	57
Anemia	22	13	4	0	9
Thrombocytopenia	15	9	8	0	18
GOT	8	1	0	0	
GPT	10	1	0	0	
Creatinine	1	0	0	0	
Anorexia	4	1	2	0	5
Vomiting	2	2	0	0	
Diarrhoea	0	1	2	0	5
AIP	0	0	1	0	2
Febrile neutropenia	0	0	1	0	2

GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; ALP = alkaline phosphatase.

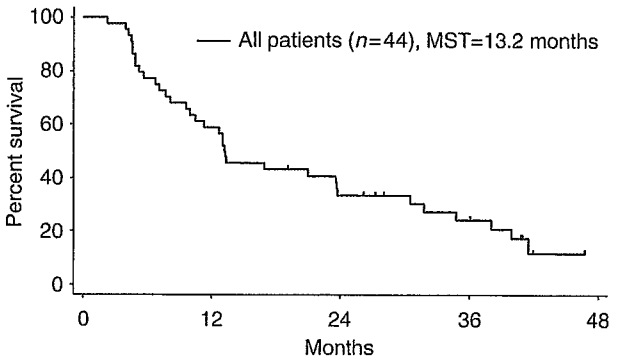

Figure 1 Overall survival. Each tick represents a patient who is alive.

DISCUSSION

Platinum-based combination chemotherapy is recommended for the treatment of advanced NSCLC patients with a good performance status (Pfister *et al*, 2004). However, the incidence of severe adverse effects induced by this combination chemotherapy is indeed more frequently observed in elderly patients than younger patients even if the subjects have good performance status (Langer *et al*, 2002). Therefore, a single agent such as vinorelbine, whose effect on prolonging survival in advanced NSCLC with elderly has been demonstrated in comparison to the best supportive care (Anonymous, 1999), is sometimes selected to treat such patients in practice. In addition, the combination of vinorelbine plus gemcitabine has been reported to be not more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC (Gridelli *et al*, 2003).

Lung cancer is primarily a disease of the elderly. More than one half of new diagnoses and more than two-thirds of annual deaths occur in patients over 65 years (Havlik *et al*, 1994; Gridelli *et al*, 1997). Although the aim of the present study was not to develop a treatment for only the elderly, the median age of the patients in this study was 74 years and 48% of the patients were 75 years or older. The reasons for this age distribution were thought to be partly due to the followings: First, the subjects of almost all previous clinical trials for chemotherapy against advanced NSCLC conducted in Japan were limited to patients under 75 years of age. Second, both UFT and gemcitabine were considered to be relatively safe anticancer agents. Third, they could be administered on an outpatient basis with no need for premedication and prehydration.

The overall response rate of the present trial using UFT and gemcitabine was 41%. In a phase I trial of this combination chemotherapy, the response rate of patients without prior chemotherapy was also reported to be 45% (Seto *et al*, 2002). This high antitumour effect may lend support to the sequence of administration of UFT and gemcitabine. In fact, an *in vitro* study has shown the sequence-dependent antitumour effects of the combination of 5-FU and gemcitabine to be seen with a maximum effect when 5-FU preceded gemcitabine (Rauchwerger *et al*, 2000). Since the 5-FU concentration in blood reaches a steady state 5 days after the start of UFT administration (Ho *et al*, 1998), the administration of gemcitabine on days 8 and 15 is considered to be most appropriate.

Since the recent randomised trial demonstrated that gemcitabine plus carboplatin produced a significantly higher response rate and survival rate than gemcitabine alone in advanced NSCLC patients including a substantial proportion of elderly patients (37% of patients >70 years old), the combination chemotherapy using gemcitabine and carboplatin (Sederholm, 2002) may also be considered to be a suitable chemotherapy regimen for the treatment of elderly patients. The response rate and median survival time in the combination chemotherapy group has been reported to be 30% and 10 months, respectively. Grade 3 or 4 nonhaematologic toxicity was observed in 26% of the patients, while grade 3 and 4 thrombocytopenia was reported in 24% each of patients, respectively. A toxicity profile in the elderly has not yet been reported.

In the present phase II trial of 44 patients with a median age of 74 years, including 21 patients who were 75 years or older, the response rate was 41% and the median survival time was 13.4 months. These observations suggest that this combination chemotherapy is also worthy of further investigation for the treatment of all NSCLC patients including the elderly. In addition, it should be confirmed whether or not this combination regimen is equally effective in ethnic groups other than Japanese.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

A Prospective Japanese Study of the Association between Personality and the Progression of Lung Cancer

Jun Nagano[1], Yukito Ichinose[2], Hiroshi Asoh[2], Jiro Ikeda[2], Akira Ohshima[3], Nobuyuki Sudo[4] and Chiharu Kubo[4]

Abstract

Objective To examine predictive values for the effect of the "Type 1" (hopeless and emotion-suppressive, cancer prone), "Type 4" (autonomous, healthy), and "Type 5" (rational/antiemotional, cancer prone) personalities proposed by Grossarth-Maticek on the prognosis of lung cancer patients.

Methods 68 lung cancer patients were scored on the Types 1, 4, and 5 personality scales of the Short Interpersonal Reactions Inventory and were followed until the date of death or were censored at a maximum of 5.7 years after entry.

Results The stage at diagnosis tended to be higher in patients with a high Type 1 or a low Type 4 score. A univariate Cox proportional hazards model showed that a high tendency toward Type 1 or Type 5 was related to an increased hazard of death. Adjustment for age, performance status, and stage, however, attenuated the relation to Type 1, leaving only Type 5 as a significantly related personality factor.

Conclusion A high Type 5 tendency may predict poor survival in lung cancer patients, whereas Types 1 and 4 may not be independent predictors.

Key words: prospective study, lung cancer, personality, stress, survival

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INTRODUCTION

Lung cancer is one of the most common cancers worldwide (1). In Japan, the mortality rate from lung cancer has constantly increased from the late 1900s, and now is the leading cause of cancer death for men and the second leading cause for women (2). The cure rate of lung cancer is poor and has little improved in the past two decades, especially for patients with advanced disease (3).

Several psychosocial factors have been linked to the onset and progression of cancer (4-6). Hopelessness/helplessness and suppression of negative emotions are personality factors that have been associated with cancer in previous prospective studies, especially studies examining their effects on cancer progression, although much more research will be necessary before a definite conclusion can be made (4). The above factors have been linked to cancer progression mainly in studies of breast cancer (7-11) or cancer of mixed sites (12, 13). However, little has been reported on lung cancer, except for recent studies of a personality relevant to emotional suppression (14) and of optimism, which may be the opposite of hopelessness/helplessness (15).

Grossarth-Maticek and colleagues conceptualized a disease-prone/healthy personality theory including a notion of six personality types, "Type 1" to "Type 6" (see Appendix) (16-19). This theory began with four types, Types 1 to 4, with the other two types added later (17). Types 1, 4, and 5, which include either one or both emotional suppression and hopelessness/helplessness as elements, have been linked to cancer. Type 1 is an "object dependent" personality that has a highly valued object (person or condition) through which well-being is chronically swayed toward hopelessness/helplessness and depression by withdrawal of the ob-

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ject. It is also characterized by altruistic behaviors and inhibition when expressing negative emotions and personal needs. Type 4 is an "autonomous" personality, the opposite of object dependence, and expresses personal needs in appropriate ways to obtain wellbeing. Type 5 is characterized by an extreme tendency toward "rational and antiemotional" reactions to stress, which also is an aspect of suppression of negative emotions. In cohort studies that began in Yugoslavia in the 1960s and in West Germany in the 1970s, Type 1 was shown to be prone to cancer, Type 4 was the most healthy and resistant to diseases, including cancer and cardiovascular disease (16), and Type 5 (17), as is its original concept of the rationality/antiemotionality (R/A) personality (20) was also prone to cancer. Not many studies have so far independently addressed the relation between these personalities and cancer risk (21-25), and no study has explored their possible relations with cancer progression.

In 1998, lung cancer patients hospitalized in a regional cancer center in Japan were asked to complete a Japanese version of the Short Interpersonal Reactions Inventory (SIRI) (26). The SIRI is a self-report questionnaire that consists of six scales corresponding to Types 1 to 6 (17). This data was used as part of a case-control study to examine the associations between Types 1 to 6 and the risks of lung cancer and myocardial infarction (24). The results failed to support the hypothesis that Types 1 and 5 were positively associated and Type 4 was inversely associated with lung cancer risk. These findings, however, did not exclude the possibility that Types 1 and 5 increase, while Type 4 decreases, the hazard of death in lung cancer patients. In view of the paucity of data on personality and lung cancer progression (14, 15), we studied the relationships of Types 1 to 6 personalities and the survival of lung cancer patients over a follow-up period of up to 5.7 years.

Table 1. Demographic, Behavioral, and Clinical Characteristics of the Subjects (N=68)

Characteristics		%
Gender	Male	74
	Female	26
Age	<40 years	3
	40-49 years	18
	50-59 years	41
	60+ years	38
Education	Junior high school	22
	High school	46
	Junior college or equivalent	10
	College or higher	22
Marital status	Married	75
	Not married	25
Smoking	Never	26
	Past	3
	Current	71
Time since diagnosis	0-4 weeks	49
	5-8 weeks	34
	9-12 weeks	7
	13+ weeks	10
Histology	Small cell carcinoma	15
	Non-small cell carcinoma	85
Performance status	0	74
	1	21
	2	6
Stage	I	29
	II	4
	IIIA	16
	IIIB	19
	IV	31

METHODS

Subjects

Eligible lung cancer patients in a consecutive series were asked to participate in the study during their admission to the National Kyushu Cancer Center in Japan from February to December 1998. Criteria for enrollment were age of 70 years or under and not too severely ill to complete a self-administered questionnaire without assistance. Participating patients were asked to complete a set of questionnaires including the SIRI. The results of a case-control study using the baseline data of these subjects were reported previously (24). Follow-up was terminated in January 2004, and data was censored at that time. Demographic and clinical data were obtained from medical records.

The Short Interpersonal Reactions Inventory (SIRI)

The SIRI is a self-administered questionnaire developed to measure the 6 Grossarth-Maticek personality types (17). All the participants completed a Japanese version of the SIRI, for which psychometrical reliability and validity were reported elsewhere (26). The SIRI contains 70 items with a dichotomous answer, "yes" or "no", of which 10 items correspond to each of the six types, except for Type 4 which is represented by 20 items, including 10 reverse items. The score for each type is the number of positive responses, except for the Type 4 score which is divided by two so that all types reflect a score between 0 and 10.

Analysis

Survival was measured from the date of recruitment through the date of death or was censored at the last contact date for surviving patients. Demographic, behavioral, and clinical factors including sex, age (continuous), marital status (married, not married), education years (12 years or less, 13 years or over), smoking status (current smoker, never/past smoker), time since diagnosis (0-4 weeks, 5+ weeks), histology (small cell carcinoma, other types), and stage (ordinal) were considered as known or potential risk factors for death in the lung cancer patients. Associations

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Table 2. Association Between Peraonality Factors and Demographic, Behavioral, and Clinical factors

Characteristics	Grossarth-Maticek personality											
	Type 1				Type 4				Type 5			
Score	0-3	4-5	6+		0-6.5	7-8	8.5+		0-5	6-7	8+	
N	27	20	21	p[a]	21	28	19	p[a]	24	26	18	p[a]
Male (%)	56	85	86	0.0243	86	71	63	0.26	58	81	83	0.11
Age, mean (years)	54.4	59.5	56.1	0.13[b]	54.5	56.0	59.2	0.21[b]	52.2	57.1	61.2	0.0021[b]
Marital status: married (%)	70	75	81	0.70	62	79	84	0.23	71	85	67	0.34
Education years 13+ (%)	33	20	43	0.29	38	36	21	0.46	42	19	39	0.19
Current smoker (%)	56	85	76	0.07	76	68	68	0.79	63	77	72	0.53
Time since diagnosis, mean (weeks)	7.4	7.4	9.5	0.55[c]	10.1	7.4	6.6	0.39[c]	10.1	7.4	6.3	0.49[c]
Histology: small cell carcinoma (%)	7	10	24	0.22	14	7	21	0.38	13	12	17	0.88
Performance status 1-2 (%)	26	15	38	0.24	29	29	21	0.82	21	19	44	0.13
Early stage disease (stage I) (%)	41	45	0	0.0004[d]	10	36	42	0.0449[d]	29	27	33	0.94[d]

[a]P-values were based on the chi-square test, [b]analysis of variance, [c]Kruskal-Wallis test, or [d]Fisher's exact test.

between these factors and the SIRI scores were examined by either the student's t-test or one-way analysis of variance, as appropriate. A univariate or multivariate Cox proportional hazards model was used to examine the associations between a factor(s) of interest and survival. Of these demographic and clinical variables, those found to be associated with survival with a p-value <0.1 on univariate analysis were adjusted for each other in a multivariate model. Factors related to survival with a p-value <0.1 in the multivariate model were then retained as variables to be considered in exploring the relationship of the SIRI scores with survival. According to the SIRI scores, the subjects were categorized into tertiles. Hazard ratios of death with a 95% confidence interval for the intermediate and highest score categories were estimated in comparison with the lowest category, and a linear trend of association was tested, with or without adjustment for covariates as determined above. Computations were done using the SAS software (UNIX version release 8.2, SAS Institute Inc.). Reported p-values were two-sided, and p-values less than 0.05 were regarded as statistically significant.

RESULTS

Of the 101 eligible patients, 95 agreed to participate in the study and signed a written consent form. For the present longitudinal analyses, 25 patients who at entry were admitted for a second or later admission for the treatment of relapse or re-growth of the disease were excluded. Data on survival status were obtained for the remaining 70 patients who were in their first admission. Also included were two patients who had been transferred from another hospital for the purpose of radiotherapy. Of these 70, two were excluded who had at first been strongly suspected of having primary lung carcinoma, but the diagnosis was not confirmed on further examinations. All patients had been informed of their diagnosis before the time of recruitment.

Demographic, behavioral, and clinical characteristics of the subjects and their associations with the personality variables at baseline

Table 1 summarizes demographic, behavioral, and clinical characteristics of the studied patients. Nearly 80% of the patients were 50 years or older at entry, and 74% were male. Approximately 30% had an education of junior college or higher, 13+ years, 75% were married and living with their spouse, and 71% were current smokers. Time from the cancer diagnosis through recruitment was 12 weeks or less for most (90%) patients. Most (85%) patients had a histological diagnosis of non-small cell carcinoma, 95% were at the Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and fewer than 30% had an early stage disease according to the International Staging System (27). During the follow-up period, 40 patients died and 28 were censored. The median time of survival was 0.8 (range 0.2-5.4) years for diseased subjects, and the median follow-up was 5.1 (range 4.7-5.7) years for survivors.

Table 2 shows the personality scores in relation to demographic and clinical characteristics at baseline. The percentage of men in the lowest Type 1 category was lower than that of the higher two categories. Age tended to increase linearly as the Type 5 score increased. Marital status, education level, smoking status, time since diagnosis, histology, and PS were not associated with any of the three personality types. Regarding the disease stage, there were notable associations. None of the patients in the high Type 1 category were diagnosed as having an early stage disease (stage I), while more than 40% were in stage I in the lower two Type 1 categories. Conversely, the low Type 4 category included a smaller percentage of early-stage patients than the two higher Type 4 categories. These associations of disease stage with Types 1 and 4 were statistically significant. Type 5 was

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Table 3. Association Between Personality and the Hazard of Death of Lung Cancer Patients

			Unadjusted (crude) HR		Adjusted HR[a]	
Scale	Score	N	HR (95%CI)	p trend	HR (95%CI)	p trend
Type 1	0-3	27	1.00 (ref.)		1.00 (ref.)	
	4-5	20	0.74 (0.31-1.79)		0.51 (0.20-1.26)	
	6+	21	3.26 (1.59-6.69)	0.0021	1.73 (0.80-3.73)	0.16
Type 2	0-1	34	1.00 (ref.)		1.00 (ref.)	
	2-3	18	1.18 (0.60-2.34)		0.98 (0.48-2.00)	
	4+	16	1.27 (0.87-1.86)	0.18	0.97 (0.64-1.48)	0.90
Type 3	0-1	18	1.00 (ref.)		1.00 (ref.)	
	2-3	25	0.63 (0.28-1.42)		0.86 (0.38-1.95)	
	4+	25	0.95 (0.44-2.06)	0.96	1.08 (0.48-2.40)	0.83
Type 4	0-6.5	21	1.00 (ref.)		1.00 (ref.)	
	7-8	28	0.70 (0.35-1.42)		0.63 (0.29-1.35)	
	8.5+	19	0.57 (0.25-1.31)	0.18	0.65 (0.27-1.55)	0.29
Type 5	0-5	24	1.00 (ref.)		1.00 (ref.)	
	6-7	26	1.75 (0.79-3.86)		2.20 (0.96-5.03)	
	8+	18	3.21 (1.41-7.30)	0.0054	2.79 (1.13-6.86)	0.0221
Type 6	0	24	1.00 (ref.)		1.00 (ref.)	
	1	22	0.94 (0.43-2.08)		0.75 (0.32-1.74)	
	2+	22	1.36 (0.65-2.81)	0.42	1.07 (0.49-2.34)	0.85

HR: hazard ratio; CI: confidence interval. [a]Adjusted for age, performance status, and stage.

not related to the stage at baseline. None of the other scores of Types 2, 3, and 6 were appreciably associated with any demographic or clinical characteristic at baseline (data not shown).

To search for reasons that would explain the relation between stage and Types 1 and 4, we studied the charts for any two factors that may represent health-care behaviors that had led to diagnosis. First, we classified the cues to diagnosis into three categories, "asymptomatic and found by check-up", "found by symptoms such as cough and chest pain", and "incidental, e.g., found when patient saw a doctor for reasons unrelated to cancer". Second, we calculated the time that it took from the cue to the time of diagnosis. These factors were examined in relation to the Type 1 and 4 categories. However, no two factors were significantly associated with those personalities (data not shown).

The personality factors and survival at follow-up

Of the demographic, behavioral, and clinical factors, gender ($p=0.0287$), age ($p=0.088$), PS ($p<0.0001$), and stage ($p<0.0001$) were related to survival by univariate analyses, while education level, marital status, smoking status, time since diagnosis, and histology were not. A multivariate Cox proportional hazards model including gender, age, PS, and stage revealed that increasing age ($p=0.0226$), poorer PS ($p<0.0018$), and a more advanced stage ($p<0.0001$) were associated with a higher hazard of death, whereas gender was no longer predictive of prognosis ($p=0.11$). Therefore, age, PS, and stage were adjusted for in the subsequent analyses of the personality factors.

Table 3 shows the associations of the personality factors with the survival of lung cancer patients. In the univariate analyses, the highest Type 1 category was significantly associated with an increased hazard of death when compared with the lowest category. The crude hazard of death significantly increased as the score of Type 5 increased. When age, PS, and stage were adjusted, however, the association with Type 1 personality became unclear, and only the positive association of Type 5 to survival remained significant. The adjusted hazard ratio of death for the patients in the high Type 5 category was approximately 2.8 as compared to that of the low category. Types 2, 3, and 6 were not materially associated with survival with or without adjustment for the covariates. In Fig. 1, the Kaplan-Meier survival curves are shown according to the three categories of Type 5 scores.

DISCUSSION

This study addressed the question of whether or not the personalities proposed by Grossarth-Maticek, especially the Type 1, 4, and 5 personalities which have been associated with cancer risk in healthy populations (16, 17, 20), can be predictive of the prognosis of lung cancer patients. Univariate analyses found a high tendency for Types 1 and 5 to be related to an increased hazard of death, but adjustment for other risk factors attenuated the relation to Type 1, leaving

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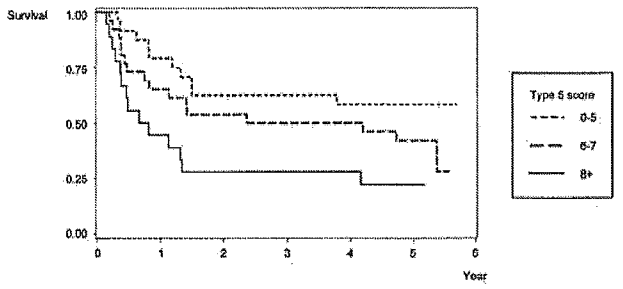

Figure 1. Survival curvers of lung cancer patients according to low, medium, or high Type 5 scores

only Type 5 as a significant, independent predictor of survival for lung cancer patients.

The Type 5 personality, characterized by "rational and antiemotional" reactions to stress, was formerly called the R/A personality and later re-conceptualized into the six type personalities. The R/A represents an extreme tendency to rationalize conflicts or frustrations and to suppress emotional reactions as represented by the SIRI item "when people make emotional demands on me, I usually react only rationally, never emotionally", and can be considered a form of the suppression of negative emotions. Few studies have independently examined this unique personality construct in association with cancer risk. A cohort study in the Netherlands examined the rationality and the antiemotionality factors separately, and found that a high antiemotionality score was associated with an increased risk of breast cancer (28). A cohort study in Japan, however, found that the risk of mortality from cancer of men scoring in the middle range of the R/A scale was lower than for those scoring low on the scale (25). To our knowledge, no previous data is available on the association between the Type 5 and R/A personalities and cancer progression.

Regarding the suppression/expression of negative emotions as a more common construct, several studies have examined this personality factor in relation to cancer progression. Most focused on breast cancer, and some (7, 10, 11), albeit not all (8, 9), agreed that suppressing or controlling negative emotions worsened the prognosis of breast cancer patients. To the contrary, "expression of negative affect" (7) and "expressing emotions" (10) were associated with a better prognosis in breast cancer. As for lung cancer, Nakahara et al found that a better survival was associated with a personality characterized by high "Free Child" and low "Adapted Child" scores (14).

Significant associations were found between the stage at baseline and the scores of Types 1 and 4. None of the patients with an early stage disease were categorized into the high Type 1 category, and only a few into the low Type 4 category. It is possible that people with a high Type 1 or a low Type 4 tendency may be much more negative than others toward taking a lung cancer screening, or that these people may be more hesitant to visit a clinic for further examination after preliminary tests indicating lung cancer. Supplemental analyses, however, did not yield evidence to support these hypotheses, which may have accounted for the associations between baseline stage and Types 1 and 4. Other hypotheses may include the possibility that the chances of cancer progression from an early to an advanced stage are higher in people with a high Type 1 or low Type 4 tendency, or that the cancer progression is more rapid, thereby creating a lower chance of having a disease discovered at an earlier stage.

It should be noted that all of the present study participants had been informed of their diagnosis before they completed the SIRI. In a population-based prospective study in the Netherlands, Bleiker et al examined the possible differences in personality traits between before and after a diagnosis of breast cancer. They found a significant decrease in the "rationality", "emotional expression-out", and "emotional-control" scores from before to after the diagnosis (29). In the present sample, although the scores for the personalities were not related to the time since diagnosis to entry, it is impossible to preclude the possibility that the patients' personalities as measured by the SIRI had changed between before and just after the diagnosis. The present associations of Type 5 with survival and Types 1 and 4 with stage at baseline may not be able to be generalized to lung cancer patients for whom a diagnosis has not yet been made or who are unaware of the diagnosis.

The present study has several limitations. The small sample size did not allow analyses with stratification by factors such as stage, gender, and histology (small cell carcinoma or non-small cell carcinoma), although the association between the Type 5 personality and survival may differ according to these factors. In addition, the mechanisms which may explain the observed association with the Type 5 personality were not clarified. Patients with different personalities may differently decide on the choice of treatments, or respond differently to a certain treatment regimen, and such diversity may affect the clinical course. The present study could not consider the possible effects of such complex treatment factors. Also, it did not examine immunological parameters that might link personality factors with survival of lung cancer patients (30-32). Nevertheless, this is the first report specifically addressing if Types 1, 4, and 5 can be of prognostic value for persons suffering from a malignancy, and would confer evidence to the notion that personality factors are related to the prognosis of lung cancer.

In summary, the current prospective data suggested that a stronger Type 5 tendency may increase the hazard of death of lung cancer patients. Types 1 and 4 personalities were not an independent risk factor for death, although they might be associated with the stage at diagnosis. The current findings should be confirmed in future studies of a larger scale that examine behavioral and biological factors that would explain the association between the Type 5 personality and cancer progression.

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Appendix. Summarized Characteristics of the Grossarth-Maticek Personality Types and Traits to which they are Prone

Personality	Characteristics	Proneness
Type 1	Dependence on withdrawn objects: - one's well-being is dependent on a withdrawn, highly-valued object (person or situation), - chronically experience hopeless/helpless and depressive feelings, - altruistic behavior and inhibition to express negative emotions and personal needs.	To cancer
Type 2	Dependence on disturbing objects: - one's well-being is constantly threatened by a disturbing, annoying objects (person or situation), - chronically experience feelings of anger, hostility, aggression, and excitement, - feel that frustrating situations are unavoidable.	To cardiovascular disease
Type 3	Ambivalent behavior: - oscillate between the positive and negative aspects of an object (person or situation), - sometimes idealize the object, sometimes devalue it, and fail to reach any integration, - express one's emotion and needs in inadequate and ambivalent ways.	To chronic anxiety
Type 4	Autonomic behavior: - maintain autonomy by flexibly regulating distance to objects (person or situation), e.g., letting a withdrawing object go or keeping distance from an annoying object, - self-regulate behaviors, including expression of emotions and needs, so that they lead to the achievement and maintenance of well-being.	To being healthy
Type 5	Rational and antiemotional behavior: - constantly cope with stress by appeals to reason and logic, never to emotional behaviors, - suppress emotional reactions and behave rationally even in frustrating interpersonal communications.	To cancer, cardiovascular disease, and depression
Type 6	Antisocial behavior: - egocentric, antisocial, and psychopathic behaviors, - express emotions and needs in inadequate and non-conforming ways.	To criminal behaviors and drug addiction

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Phase I Study of Amrubicin Hydrochloride and Cisplatin in Patients Previously Treated for Advanced Non-small Cell Lung Cancer

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Phase I Study of Amrubicin Hydrochloride and Cisplatin in Patients Previously Treated for Advanced Non-small Cell Lung Cancer

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Objective: A single-center phase I trial was designed to determine both the dose-limiting toxicities and the maximum tolerated dose (MTD) for amrubicin hydrochloride in combination therapy with cisplatin for advanced non-small cell lung cancer (NSCLC) patients with prior chemotherapy.

Methods: Eligible patients received amrubicin and cisplatin on days 1 through 3 every 3 or 4 weeks. Cisplatin was administered at a fixed dosage of 20 mg/m^2 while the administered dose of amrubicin was started at 20 mg/m^2. Each group comprised 3 or 6 patients. When dose limiting toxicities were noted in three or more of six patients at a particular level, that level was estimated to be the MTD.

Results: Fifteen patients were enrolled in this study, including 5 males and 10 females, with a median age of 57. The dose limiting toxicities included grade 4 neutropenia which lasted 4 or more days and febrile neutropenia. The non-hematologic toxicities were well managed and rarely severe. The MTD of amrubicin in this combination regimen was estimated to be 30 mg/m^2. A partial response was observed in 4 of 15 patients (27%).

Conclusions: The recommended dose was thus determined to be 25 mg/m^2 amrubicin with 20 mg/m^2 cisplatin for 3 consecutive days. A phase II study is currently underway.

Key words: amrubicin hydrochloride – cisplatin – non-small cell lung cancer – phase I study – prior chemotherapy

INTRODUCTION

Platinum-based combination chemotherapy has been the standard first line treatment for advanced non-small cell lung cancer (NSCLC) (1). The median survival time (MST), however, ranges from 7.4 to 8.1 months in patients treated with platinum-based combination chemotherapy and this treatment still remains unsatisfactory regarding its overall clinical effectiveness (2,3). On the other hand, docetaxel monotherapy has shown an approximately 7% response rate, thus leading to an average increased survival time of 3 months and a better quality of life when used as a second-line therapy in patients with advanced NSCLC, in comparison to the best supportive care (4,5). Based on these results, docetaxel monotherapy is widely regarded as a standard second-line treatment (6,7). Recently, pemetrexed has been shown to have the same effect as docetaxel in terms of the response rate and survival (8). In addition, epidermal growth factor receptor-tyrosine kinase inhibiting drugs such as gefitinib and erlotinib have also been approved for the treatment of NSCLC patients with prior chemotherapy (9,10). Although we now have several choices for the treatment of patients with a progressive disease either during or after undergoing other types of chemotherapy, the number of effective drugs for such patients still remains limited.

Amrubicin hydrochloride, which is a totally synthetic 9-aminoantracycline, is metabolically activated by a liver enzyme to amrubicinol. Amrubicin is reported to have either an equivalent or a stronger anti-tumor effects in comparison with doxorubicin in nude mice transplanted with human tumor cells (11–13). The anti-tumor mechanism of amrubicin itself and its active form, amrubicinol, is due to the break-down of DNA strands during the stabilization process of DNA-topoisomerase II cleavable complex (14). In a phase I trial of the intravenous administration of amrubicin for 3 consecutive days at 3-week intervals in patients without prior chemotherapy, the maximum tolerated dose (MTD) and the recommended dose were estimated to be 50 mg/m^2 and 45/m^2, respectively. The major dose limiting toxicity (DLT) was myelosuppression (15). A subsequent phase II trial in patients with advanced NSCLC without prior chemotherapy demonstrated a response rate of 23% with a MST of 9.4 months (16).

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These findings suggest that amrubicin may be a promising anti-tumor agent for treatment of NSCLC.

To our knowledge, no clinical trials using amrubicin in previously treated advanced NSCLC patients have yet been conducted. Since the main toxicity of amrubicin is myelotoxicity, it is expected that the administration of a full dose of amrubicin will not be tolerable for previously treated NSCLC patients. A synergistic or additive anti-tumor effect between cisplatin and amrubicin has been reported (17,18). Since the major toxicity of cisplatin is not only non-hematologic but it can also be reduced by dividing up the administered doses, the concurrent combination of amrubicin and cisplatin of a low dose may possibly augment the anti-tumor activity of amrubicin without any severe myelotoxicity, even in patients who have already received other types of platinum-based chemotherapy as prior treatment (19,20). Based on this hypothesis, we conducted a phase I trial to find the MTD of amrubicin which was concurrently administered with a low dose of cisplatin, 20 mg/m^2, for 3 consecutive days, in advanced NSCLC patients with a history of prior chemotherapy.

PATIENTS AND METHODS

ELIGIBILITY

Patients with either cytologically or histologically confirmed advanced NSCLC who demonstrated disease progression either during or after a prior chemotherapy were eligible. The eligibility criteria also included the following factors: an age ranging from 20 to 75 years; an Eastern Cooperative Oncology Group performance status $\leq$1; a life-expectancy of $\geq$3 months; no chemotherapy or radiation therapy within 4 weeks of treatment; an adequate hematopoietic status [absolute neutrophil count (ANC) $\geq$2000/μl, hemoglobin level $\geq$10 g/dl, platelet count $\geq$100 000/μl], hepatic (transaminases $\leq$2 $\times$ institutional normal upper limit, total bilirubin $\leq$1.5 $\times$ institutional normal upper limit) and renal (creatinine $\leq$ institutional normal upper limit) functions; either measurable or evaluable but nonmeasurable disease such as numerous small sized pulmonary metastases, $PaO_2 \geq 60$ torr; and left ventricle ejection fraction of 60% or more based on ultrasound cardiogram. Patients gave their written informed consent before treatment. The protocol was approved by the institutional review board of the National Kyushu Cancer Center.

DOSAGE AND DRUG ADMINISTRATION

Amrubicin and cisplatin were administered on days 1 through 3 of each 3 or 4-week cycle. Cisplatin was administered at a fixed dosage of 20 mg/m^2/day for 3 consecutive days while amrubicin was started at 20 mg/m^2/day for 3 consecutive days and then increased by 5 mg/m^2/day until reaching the MTD. Amrubicin was dissolved in either 20 ml of a 5% glucose solution or saline for the intravenous injections. Following the administration of amrubicin, cisplatin was administered intravenously together with 1500 ml of hydration. At least, two cycles of this combination chemotherapy were administered every 3 or 4 weeks unless either a disease progression or unacceptable toxicity occurred. The MTD was defined as the lowest dose at which three or more of six patients experienced DLT during the first course of the treatment. At least three patients were treated at each dose level that did not result in DLT. If one or two of the initial three patients developed DLT, then three additional patients were entered at the same dose level. DLT was defined as follows; grade 4 leukopenia or neutropenia lasting for 4 days or more; an ANC of $\leq$1000/μl associated with fever ($\geq$38.5°C), a platelet count of $\leq$20 000/μl; and a grade 3 or greater non-hematological toxicity (excluding anorexia, nausea and vomiting). The prophylactic use of growth factors was not permitted. However, at the discretion of the treating physician, granulocyte colony stimulating factor was used for the treatment of febrile neutropenia and grade 4 neutropenia. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria Version 2.0.

PRETREATMENT AND FOLLOW-UP STUDIES

The performance status, the interval toxicities, concurrent medications, physical examinations, complete blood counts, electrolytes and chemistries were evaluated before treatment and weekly thereafter. Pretreatment studies also included chest radiography, computed tomography scans to evaluate all sites of disease, an electrocardiogram and ultrasound cardiogram. Computed tomography scans were repeated every 4 weeks. A complete response was scored if there was a disappearance of all active disease on two measurements separated by a minimum period of 4 weeks, and a partial response required at least a 50% reduction in the sum of the product of the bidimensional measurements of all lesions documented separated by at least 4 weeks. Any concurrent increase in the size of any lesion by $\geq$25% or the appearance of any new lesion was considered to indicate progressive disease. No change was defined as the absence of a partial or complete response without progressive disease being observed for at least 4 weeks after the start of the treatment.

RESULTS

GENERAL

Between July 2003 and March 2004, 15 patients were enrolled in this study. Table 1 shows the patient characteristics. The study included 5 males and 10 females with a median age of 57 years ranging from 51 to 72. Five and 10 patients had a performance status of 0 and 1, respectively, and most patients histologically had adenocarcinoma. Concerning previous treatments other than chemotherapy, four patients each underwent either surgery or thoracic radiotherapy. Regarding prior chemotherapy, platinum-based chemotherapy was performed in 14 patients while one patient received chemotherapy using gemcitabine plus vinorelbine. The

Table 1. Patient Characteristics

	No. of patients
Sex	
Male	5
Female	10
Age (years)	
Median	57
Range	51–72
Performance status (ECOG)	
0	5
1	10
Histology	
Adenocarcinoma	13
Others	2
Previous treatment	
Chemotherapy only	7
Chemotherapy and radiotherapy	4
Chemotherapy and surgery	4
No. of prior chemotherapy regimen	
Median	2
Range	1–5

chemotherapeutic regimens most frequently used as a prior treatment were cisplatin plus gemcitabine plus vinorelbine in nine patients, cisplatin plus docetaxel in six and carboplatin plus paclitaxel in five. The number of prior chemotherapy regimens ranged from 1 to 5, with a median number of 2.

At an amrubicin dosage of 20 mg/m^2, no DLT was observed. At an amrubicin dosage of 25 mg/m^2, grade 4 neutropenia lasting 4 days or more was observed in one of the first three patients. Therefore, another three patients were treated at the same dose. Since these patients did not show any additional DLT, the dosage was then escalated to 30 mg/m^2. Grade 4 neutropenia lasting 4 days or more was observed in two of the first three patients. Therefore, another three patients were assigned to receive the treatment at the same dose. Out of those three patients, one patient developed febrile neutropenia. Therefore, DLT was observed in three of six patients at an amrubicin dosage of 30 mg/m^2. As a result, amrubicin 30 mg/m^2 was determined to be the MTD. A total of 11 and 17 cycles of the treatment were performed at a dose of 20 and 25 mg/m^2, respectively. DLT was observed in 0 of 11 cycles at 20 mg/m^2 and in 1 of 17 cycles at 25 mg/m^2.

Toxicity

Myelosuppression, especially neutropenia, was the principal toxicity of this combination chemotherapy as shown in Table 2. At the MTD (amrubicin 30 mg/m^2), all three DLTs were related to neutropenia. Two patients had grade 4 neutropenia which persisted for 4 days or more. The third patient with grade 4 neutropenia had a fever associated with neutropenia that lasted for 4 days. The other three patients at the MTD also had grade 4 neutropenia which persisted <4 days. All six patients were treated with G-CSF after grade 4 neutropenia had been found. Grade 3 neutropenia was observed in one patient at dose of 20 mg/m^2 and grades 3/4 neutropenia in two at a dose of 25 mg/m^2. The onset of neutropenia (ANC $\leq$ 1500/μl) occurred between days 9 and 21: the median time to nadir and the recovery of neutrophil count (ANC $\geq$ 1500/μl) from the nadir was 16 days (range 3–23) and 5 days (range 1–24), respectively. No grade 3 or greater thrombocytopenia was observed.

Table 2. Toxicities occurring during the first cycle

Amrubicin (mg/m^2)	20		25		30	
Cisplatin (mg/m^2)	20		20		20	
	(n = 3)		(n = 6)		(n = 6)	
NCI-CTC grade	1/2	3/4	1/2	3/4	1/2	3/4
Leukopenia	1/1	1/0	2/3	0/0	0/2	1/3
Neutropenia	0/1	1/0	0/3	1/1	0/0	0/6
Febrile neutropenia	−/−	0/0	−/−	0/0	−/−	1/0
Thrombocytopenia	1/0	0/0	2/0	0/0	1/1	0/0
Hemoglobin	1/2	0/0	2/3	0/0	2/4	0/0
Fatigue	0/0	0/0	0/0	0/0	0/3	0/0
Vomiting	1/1	0/0	2/1	0/0	4/1	0/0
AST/ALT	0/1	0/0	3/1	0/0	3/1	0/0
Creatinine	1/0	0/0	1/0	0/0	0/0	0/0

The non-hematologic toxicity was mild. The toxicities mainly included nausea/vomiting, an elevation of AST/ALT and fatigue while all of them were rated as grade 2 or less and manageable.

Antitumor Activity

A partial response was observed in four patients, no change in eight and progressive disease in three. Therefore, the overall response rate was 27% (95% confidence interval: 4–49%). Responding patients were observed at every dose level of amrubicin: 1/3 at 20 mg/m^2, 2/6 at 25 mg/m^2 and 1/6 at 30 mg/m^2. Out of four patients with a partial response, two and two patients received three cycles and four cycles of amrubicin plus cisplatin chemotherapy, respectively. The responding duration of the four patients was 62, 65, 70 and 174 days.

DISCUSSION

The present study was designed to determine the recommended dose of amrubicin by estimating the MTD for combination

chemotherapy using amrubicin and cisplatin in previously treated NSCLC patients. The MTD was estimated to be 30 mg/m^2 when cisplatin at a dose of 20 mg/m^2 was administered concurrently for 3 consecutive days. At the MTD (30 mg/m^2), all six patients had grade 4 neutropenia which resulted in DLT in a half of these patients. Based on the MTD, the recommended dose was thus determined to be 25mg/m^2. The observed hematological toxicities, except for neutropenia and non-hematological toxicities, were not severe and thus were manageable. Although this study included four patients who had previously undergone thoracic radiotherapy, neither an aggravation of radiation pneumonitis nor any acute pulmonary disorders occurred.

In lung cancer patients with no prior treatment, the recommended dose of amrubicin (days 1 to 3) has been reported to be 45 mg/m^2 while it is 40 mg/m^2 when cisplatin 60 mg/m^2 is administered on day 1 (15,21). The main toxicity of amrubicin monotherapy and the combination chemotherapy tends to be myelosuppression, especially, neutropenia. Grade 3/4 neutropenia was observed in 75% of all patients with amrubicin monotherapy and in 95% of those with the combination chemotherapy (15,16,21). Therefore, the treatment regimens described above are considered to be intolerable in patients with prior chemotherapy whose bone marrow function has been, more or less, damaged.

In the present study, the concurrent administration of amrubicin and cisplatin of low dose for 3 consecutive days was performed based on the hypothesis that the addition of cisplatin to amrubicin may augment the anti-tumor activity of amrubicin. In an *in vitro* study using lung cancer cell lines, the addition of cisplatin to amrubicinol, which is an active metabolite of amrubicin , has been reported to not only enhance the inhibitory activity of topoisomerase II by amrubicinol but also to increase the formation of the DNA intestrand cross by cisplatin (18). In addition, the combination treatment with cisplatin has been shown not to alter the pharmacokinetics of either amrubicin or amrubicinol (21). These observations suggest that the concurrent administration of amrubicin and cisplatin may have an excellent anti-tumor activity without any unexpected severe toxicity, even in patients who had previously been administered platinum-based chemotherapy.

In conclusion, the MTD and recommended dose of amrubicin were determined to be 30 mg/m^2 and 25 mg/m^2, respectively, when cisplatin 20 mg/m^2 was administered concurrently for 3 consecutive days, in NSCLC patients who had received prior chemotherapy. The DLTs included neutropenia lasting 4 days or more, and febrile neutropenia. The overall response rate was 27%. A Phase II study is currently underway in these patients.

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