increased pack-years and a lower response rate was also shown (OR per 10-pack-year increase: 0.74, 95% CI: 0.56–0.99, $P = 0.041$).

The results of a multivariate analysis showed that "no history of smoking" ($P = 0.045$) and "no history of thoracic radiotherapy" ($P = 0.023$) were significant predictors of response. It was also suggested that younger patients tended to obtain a higher response rate ($P = 0.071$). Although female gender and adenocarcinoma were not found to be predictive factors in the multivariate analysis, sex and histological diagnosis were significantly associated with smoking history, and these variables may have canceled each other's effect on the dependent variable. The proportion of never-smokers was 69% (22/32) among the women versus 15% (10/66) among the men (correlation coefficient [r] = 0.536, $P < 0.001$), and 67% (54/81) among the patients with adenocarcinoma versus 0% (0/17) among those with non-adenocarcinoma ($r = 0.319$, $P = 0.001$). When a multivariate analysis was performed excluding smoking history as a factor, the OR of the females and patients with adenocarcinoma was 3.81 (95% CI: 1.36–10.7, $P = 0.011$) and 6.45 (95% CI: 0.76–55.6, $P = 0.087$), respectively.

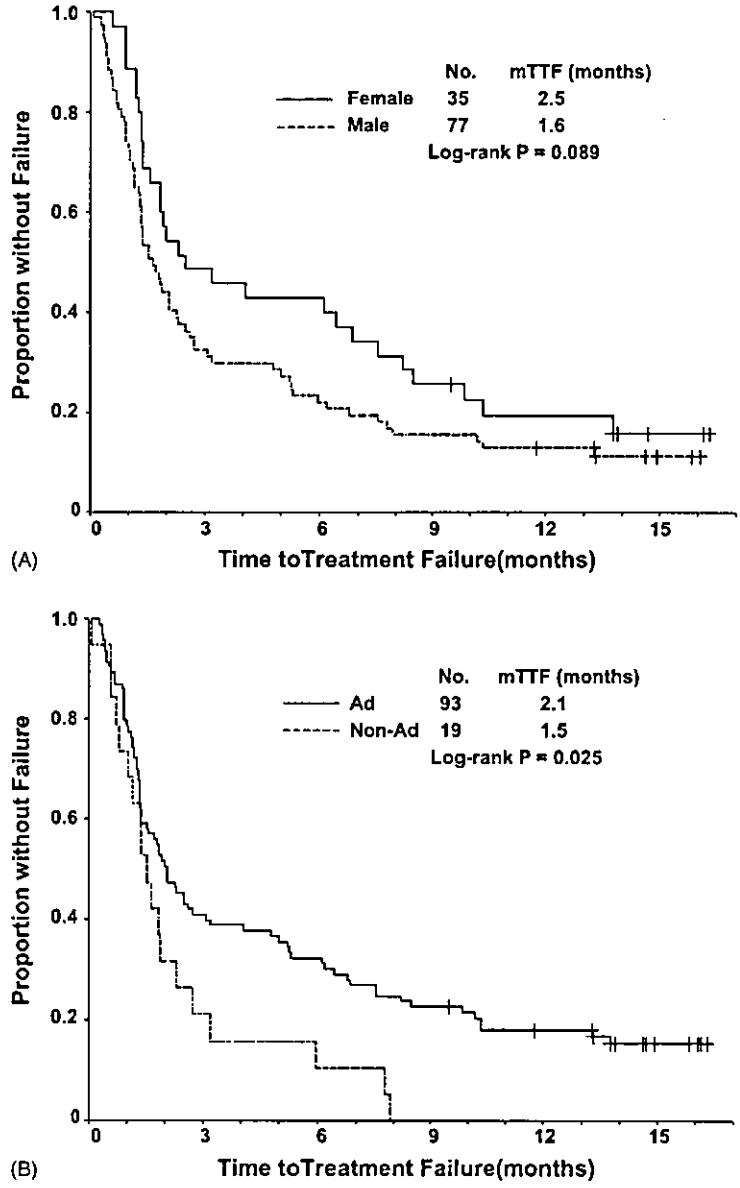

Fig. 1 Kaplan–Meier plot of time to treatment failure according to subgroups: (A) female versus male; (B) adenocarcinoma versus non-adenocarcinoma; (C) never-smokers versus moderate/heavy smokers. mTTF: median time to treatment failure, Ad: adenocarcinoma.

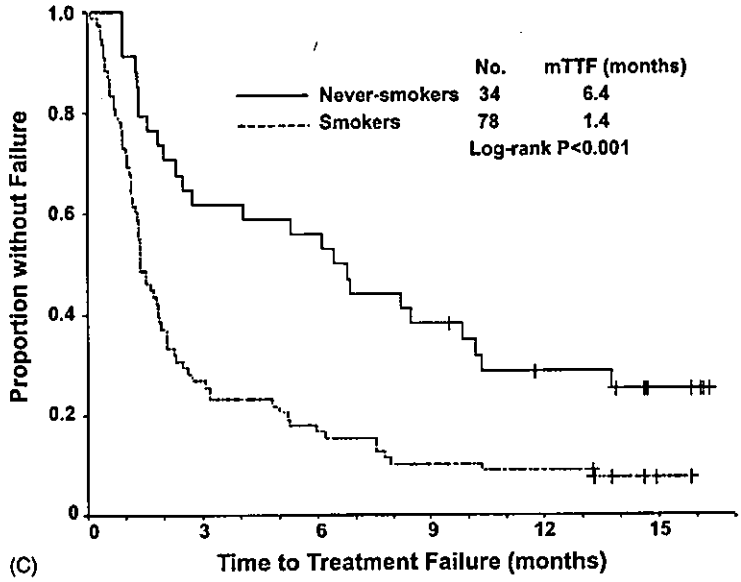

Fig. 1 (*Continued*).

The median follow-up time for survivors was 14.7 months, and ranged from 11.0 to 16.8 months. Sixty-nine patients (62%) died: 65 of disease progression and 4 of toxicity. Gefitinib treatment was terminated in 97 patients (87%) because of disease progression (68 patients), no tumor shrinkage (7 patients), toxicity (19 patients), or at the patients' request (3 patients). The median TTF and the median survival time (MST) for all patients were 1.9 and 10.7 months, respectively. The 1-year survival rate was 45%. The Kaplan–Meier plots of TTF and OS in each subgroup are shown in Figs. 1 and 2. The women had a longer TTF and OS than the men, but the difference was not significant. Patients with adenocarcinoma had a significantly longer TTF than those with non-adenocarcinoma, and "adenocarcinoma" was a marginally significant predictor of longer survival. "No history of smoking" was a highly significant predictor of longer TTF ($P < 0.001$) and longer survival ($P = 0.007$); the MST was 15.3 months in never-smokers and 8.8 months in moderate/heavy smokers.

We observed an association between efficacy and toxicity. As shown in Table 6, those who experienced skin rash or elevation in GOT/GPT levels tended to

Table 6 Association between efficacy and toxicity

	No. of patients	Response rate (%)	*P*-values*	Median survival (months)	1-year survival (%)	*P*-values†
Skin rash						
Grade 0	21	12	0.043	3.0	24	0.011
Grade 1	59	33		10.6	44	
Grade 2	29	46		15.3	66	
Diarrhea						
Grade 0	48	33	0.903	9.3	35	0.037
Grade 1–2	61	32		13.6	54	
GOT/GPT						
Grade 0	57	21	0.004	7.8	31	0.006
Grade 1	31	48		15.1	55	
Grade 2–3	18	50		Not reached	83	

* *P*-values for chi-square test between grade 0 and 1–3.
† *P*-values for log-rank test.

exhibit a response, and skin rash, diarrhea and elevation in GOT/GPT levels were significant prognostic factors of survival.

4. Discussion

Gefitinib is a promising agent for the treatment of advanced NSCLC, but risk assessment is of critical importance to using it properly. Gefitinib was thought to be a relatively safe agent at first, and physicians in Japan tended to prescribe it without careful consideration of risks. In the first 4 months after its approval, 17,000 patients began taking gefitinib, the most rapid adoption of any antitumor agent in Japan. The Ministry of Health, Labour and Welfare has estimated that the incidence of ILD was 2.2%. However, since a follow-up survey of all of the cases has not been conducted and only limited data from sporadic reports by physicians were available, many ILD cases may not have been reported, and the actual incidence may have been higher than 2.2%. Although the sample size in the present study was small, the incidence of ILD was

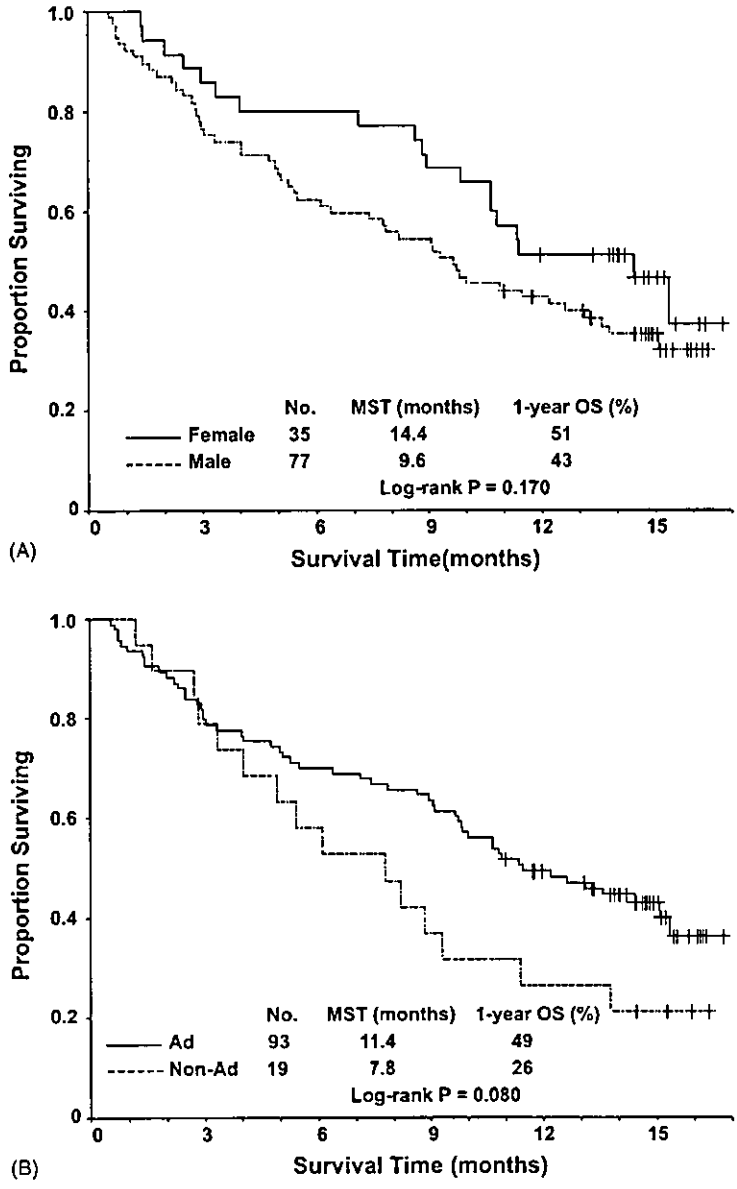

Fig. 2 Kaplan–Meier plot of overall survival according to subgroups: (A) female versus male; (B) adenocarcinoma versus non-adenocarcinoma; (C) never-smokers versus moderate/heavy smokers. MST: median survival time, OS: overall survival, Ad: adenocarcinoma.

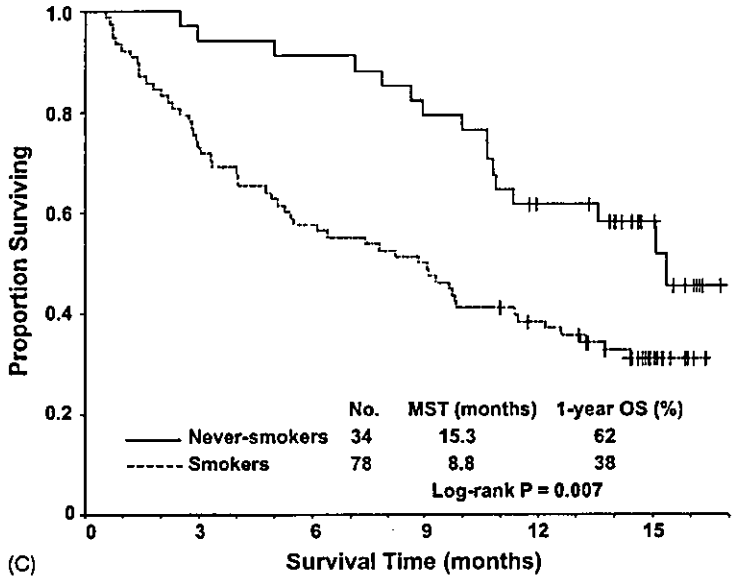

Fig. 2 (*Continued*).

as high as 5.4%. The risk of ILD appears to be around 2–5% if gefitinib is given to patients without careful risk assessment. We think that the incidence can be reduced by patient selection after a thorough risk assessment and that the proper use of gefitinib may enable great benefit, far exceeding its potential risks.

Our analysis of the risk factors for the development of ILD revealed pre-existing PF as a strong risk factor. Of the 112 patients in this study, 12 had PF at the start of gefitinib administration. Four (33%) of these patients subsequently developed ILD, 3 (25%) died as a result, and no response was seen in any of these 12 patients. A panel of experts convened by AstraZeneca Japan retrospectively analyzed 104 patients with NSCLC who developed ILD during gefitinib therapy in Japan and reported that 30 (29%) of them were diagnosed as pre-existing PF by chest X-rays or computed tomography scans taken before gefitinib administration [8]. The panel also noted that the patients with PF had a significantly higher mortality rate after the onset of ILD: it was 77% (23/30) among the patients with PF and 34% (25/74) among the patients without PF ($P < 0.001$) [8]. We conclude that gefitinib treatment may be harmful to patients with PF and recommend that gefitinib not be used if PF is apparent on the chest X-rays.

In our study, all patients were Japanese and a 33% response rate was observed. In the IDEAL 1 trial, 102 Japanese and 106 non-Japanese patients received gefitinib, and the response rate was 27.5% in the Japanese and 10.4% in the non-Japanese [5]. Whether this difference was attributable to ethnicity or an imbalance in other characteristics is unknown, but a high response rate in Japanese patients has been consistently observed in clinical practice.

Both the IDEAL 1 and 2 trials suggested "female gender" and "adenocarcinoma" as predictive factors for tumor response to gefitinib [5,6], and a retrospective analysis of gefitinib monotherapy for advanced NSCLC showed that "adenocarcinoma" (especially with bronchioloalveolar features) and "no history of smoking" were significantly correlated with response to gefitinib [9]. We observed the same tendency with a response rate of 53% in women, 38% in patients with adenocarcinoma, and 63% in never-smokers. "No history of smoking" was a significant predictive factor for response in multivariate analysis, and it was also a significant predictor of longer TTF and longer survival. Since both female gender and adenocarcinoma were significantly associated with no history of smoking, which of these characteristics are true predictive factors remains uncertain. It was also suggested that heavier smokers and male smokers specifically had a lower response rate among the patients with smoking history. Since heavier smokers tended to have a higher risk of ILD, we should carefully assess their risk-benefit ratio of gefitinib therapy before selecting therapeutic strategies.

There are some biological explanations for these clinical characteristics associated with response to gefitinib [10]. Although gefitinib inhibits the intracellular tyrosine kinase domain of EGFR, no correlation between expression of EGFR and response

has been demonstrated [11]. When EGFR and human epidermal growth factor receptor 2 (HER2) are coexpressed, HER2 is the preferred dimerization partner of EGFR, and EGFR-HER2 heterodimers have more signaling potency than EGFR homodimers [12]. Preclinical studies have indicated that tumor cell lines overexpressing HER2 or coexpressing EGFR and HER2 are sensitive to gefitinib [13–16]. Since EGFR/HER2-coexpression is more common in adenocarcinoma of the lung than in squamous cell carcinoma [13,17], the high response rate in adenocarcinoma may be attributable to it. In women, estrogens and estrogen receptors are involved in the development of NSCLC [18], and estrogens binding to its receptors upregulates EGFR and EGFR ligands [19]. The presence of estrogens and its receptors may impact EGFR signaling and the response of NSCLC to gefitinib in women. NSCLC in never-smokers may also have a different biology. Since several studies have indicated fewer mutations of the p53 and K-ras genes in never-smokers than in smokers [20,21], the relation between such tobacco-related mutations and gefitinib response should be investigated. Subgroups of patients who obtain a clinical benefit from gefitinib administration are needed to be identified more precisely, and molecular markers predictive of tumor response should be sought by using DNA microarrays and a proteomics-based approach.

Our analysis suggests that patients who suffer from skin toxicity, diarrhea, or liver toxicity have a greater clinical benefit from gefitinib treatment. A correlation between skin toxicity and survival has also been shown in a study of gefitinib for head and neck cancer [22] and in studies of erlotinib, another EGFR tyrosine kinase inhibitor [23]. Because these findings may be attributable to the responders having taken gefitinib for longer periods and the toxicities in these patients being evaluated more carefully, further studies are needed to confirm them. If the early onset of toxicities has predictive value for survival, it can be used for clinical decision making regarding continuation of gefitinib treatment.

5. Conclusion

When gefitinib is used to treat advanced NSCLC, it confers a higher risk of ILD on patients with PF and a greater clinical benefit on never-smokers, women, patients with adenocarcinoma, and patients with no history of thoracic radiotherapy. Gefitinib therapy is an important treatment option for patients with advanced NSCLC, but the proper use of it based on individual risk-benefit assessments is crucial.

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ANTI-TUMOUR TREATMENT

Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials

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KEYWORDS
Small cell lung cancer;
The elderly;
Chemotherapy;
Radiotherapy

Summary At diagnosis, 25–40% of patients with small cell lung cancer (SCLC) are 70 years of age or older, and many of them have been undertreated because of fear of excessive toxicity associated with chemotherapy. Papers retrieved by a Medline search using the key words "elderly or older" and "small cell lung cancer" and by a manual search were classified into the three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. Treatment regimens, delivery, toxicity, antitumor activity, and patient survival were reviewed in elderly patients with good and poor general condition. The standard chemotherapy regimens for the general population could be applied to elderly patients in good general condition (performance status of 0–1, normal organ function, and no comorbidity), but etoposide and carboplatin regimen with dose modification was frequently used for unselected elderly patients. A combination of full-dose thoracic radiotherapy and chemotherapy was the treatment of choice for limited SCLC in the elderly. Full cycles of chemotherapy were tolerable by 80% of the elderly patients with good general condition, but two cycles may be optimal for unselected elderly patients. Although the evidence levels based on clinical trials available today are low, these results are helpful for clinical practice and future clinical trials for elderly patients with SCLC.

Introduction

Lung cancer is currently the most common cancer in the world, and it is the leading cause of cancer death in many countries.[1,2] Small cell lung cancer (SCLC) accounts for 15–25% of all lung tumors. For treatment purposes, it is considered separately from other histological types, which are known as non-small cell lung cancer, because by the initial diagnosis SCLC has already metastastized to distant organs in 60–70% of patients, and it is highly sensitive to chemotherapy and radiotherapy. The prognosis of the disease is extremely poor. The 5-year survival rate of patients with limited disease (LD), which is a disease confined to one hemithorax that can be encompassed in a tolerable radiation field, is less than 15–25%, and most patients with extensive disease (ED), which has spread

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beyond the range of LD, die within two years after diagnosis.[3]

At diagnosis, 25–40% of patients with SCLC are 70 years old or older, and the number of patients is expected to increase, because the geriatric population is growing.[3–5] There has been a general tendency among physicians to consider aged people to always have poor tolerance for chemotherapy, and as a result many elderly cancer patients have been undertreated because of fear of excessive toxicity.[5] Thus, it is one of the immediate tasks for medical oncologists to establish treatment of SCLC in the elderly based on evidence obtained in clinical trials.

The decreases in lean body mass, hepatic blood flow, and renal function that accompany aging affect drug distribution, metabolism, and excretion. The clearance of anticancer agents commonly used for the treatment of SCLC, including cisplatin, doxorubicin, etoposide, and ifosfamide, has been shown to be decreased in the elderly.[6] Myelotoxicity is also sometimes severer in this population than in younger populations, because the absolute amount of hematopoietic marrow decreases with age. The incidence of doxorubicin-induced cardiotoxicity is also increased in the elderly, although the mechanism is unknown.[6] These age-related changes in pharmacokinetics and phamacodynamics, however, have not been fully evaluated in the treatment for SCLC in the elderly.

Studies on the treatment of SCLC in the elderly can be classified into the following three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. The first type of studies retrospectively analyzes all the elderly cases of SCLC diagnosed at an institution in a given period. They may provide information on the general aspects of elderly patients with SCLC, including performance, comorbidity, and percentages of patients treated with chemotherapy or supportive care alone. The results for outcome of treatment, however, are thought to be highly biased, because the patient populations in these studies are heterogeneous in terms of various prognostic factors. In the second type of studies, treatment outcome is retrospectively compared between an elderly group and a younger group. The patients in these studies are highly selected, because only those who meet strict eligibility criteria are included in clinical trials. Thus, the results of the analyses are understandable, but they are only applicable to the limited population of elderly patients. The most reliable and clinically useful results are obtained in the third type of studies, because the subjects can be freely defined and biases are controlled. Thus far, however, only a limited number of prospective studies on elderly patients with SCLC have been available.

The interpatient variability in activities of daily living, performance status, and comorbidity in elderly patients is so large that it is difficult to establish a standard treatment applicable to all patients. In this review, treatments for patients with good and poor general condition were summarized separately. We believe these summaries are helpful for clinical practice and future clinical trials for elderly patients with SCLC.

Methods

We retrieved papers published during the period from 1981 to 2000 by means of a Medline search using the key words "elderly or older" and "small cell lung cancer" in the Medical Subject Headings and a manual search. The papers were then classified into the three types: (1) case-series studies, (2) subgroup analyses of phase II and phase III trials by age, and (3) prospective clinical trials in the elderly. Among the retrospective studies in the first two categories, only those in which "elderly" was defined as 70 years or older were selected for the analysis. Prospective trials of infirm as well as elderly patients, however, were included in the analysis, because both populations were frequently included in the same trial. Patient characteristics, treatment regimens, treatment delivery, toxicity, antitumor activity, and patient survival were reviewed. The general clinical characteristics of the elderly SCLC patients are summarized on the basis of the results of the first type of studies. In principle, our summary of treatment for elderly patients with good performance status and no comorbidity is based on the results of the second type of studies, and our summary for unselected elderly patients is based on the third type of studies. Evidence levels are provided according to the previously described scale (Table 1).[7]

General clinical characteristics of elderly patients with SCLC

Elderly patients 70 years of age or older accounted for 26–38% (average, 31%) of all of the patients (Table 2). The percentage of limited disease ranged from 36% to 50% in both age groups. The general condition of the elderly patients was worse than in the younger patients; patients with PS 0 or 1 accounted for only 52–69% of the elderly patients, and comorbidity was noted in 63–78%. Optimal treatment, defined as four or more treatment

Table 1 Levels of evidence

I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or low false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-arm, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples

Table 2 Case-series studies on small cell lung cancer in the elderly

Authors (year)	Age	Number of patients (%)	Limited disease (%)	PS 0–1 (%)	Comorbidity (%)	Optimal treatment (%)[a]	TRD (%)	MST (month)
Nou (1996)[8]	<70	235 (68)	50	NA	NA	NA	7	11
	⩽70	110 (32)	48	NA	NA	NA	8	7
Dajczman et al. (1996)[9]	<70	231 (74)	40	80	56	44	5	9
	⩽70	81 (26)	43	52	75	23	5	6
Tebbutt et al. (1997)[10]	<70	102 (67)	46	60	NA	83	NA	No difference
	⩽70	51 (33)	49	55	63	47	4	No difference
Jara et al. (1999)[11]	<70	59 (62)	42	71	58	59	NA	8
	⩽70	36 (38)	36	69	78	39	NA	5

MST, median survival time; NA, not available; PS, performance status; TRD, treatment-related death.
[a]Optimal treatment was defined as four or more treatment cycles, relative total dose of 85% or higher, or no definition described.

cycles, relative total does of 85% or higher, or no definition available, was delivered to 23–47% of the elderly patients compared with 44–83% of the younger patients. The incidence of treatment-related death and patient survival, however, did not differ between the two age groups.

Chemotherapy for elderly patients in good general condition

Among elderly lung cancer patients, 10–30% are in good general condition without comorbidity,[9–13] and the standard chemotherapy for the general population, including cyclophosphamide, doxorubicin and vincristine (CAV), cisplatin and etoposide (PE), and CAV alternating with PE regimens, can be given to this population (Evidence level, IV). Subgroup analyses of phase II and phase III trials of SCLC by age showed that myelosuppression and doxorubicin-induced cardiotoxicity were severer in the elderly patients than in the younger patients, and that their incidence of treatment-related death tended to be higher. About 80% of elderly patients, however, received optimal treatment, and their survival was comparable to that of younger patients (Table 3).[14–16] Thus, the standard chemotherapy should be tried in these patients, although a reduction in treatment cycles and chemotherapy dose, or prolongation of treatment intervals may be needed more often than in younger patients.

Chemotherapy for unselected elderly patients

The standard chemotherapy for younger patients is not indicated for 70–90% of elderly patients because of poor performance status or the presence of complications. Oral etoposide and teniposide has been tried in these patients, but randomized trials showed that it was more toxic and had no survival benefit over the standard chemotherapy (Table 4).[17,18] A randomized trial of two-drug

Table 3 Subgroup analyses of phase III trials of small cell lung cancer by age

Authors (year)	Treatment	Age	Number of patients	Limited disease (%)	PS 0–1 (%)	Optimal treatment (%)[a]	Grade 3–4 toxicity (%)	TRD (%)	MST (month)
Paccagnella et al. (1996)[14]	CAV–PE (±TRT)	<70	254	58	ND	RDI 78	NA	3	12
		⩽70	32	56	ND	RDI 67	NA	9	12
Siu et al. (1996)[15]	CAV–PE (±TRT)	<70	520	100	88	92	Neutropenia[b] (60) Thrombocytopenia (10) Cardiac (0.2)	2	15
		⩽70	88	100	84	82	Neutropenia[b](64) Thrombocytopenia[15] Cardiac (3)	5	13
Yuen et al. (2000)[16]	PE+TRT	<70	331	100	96	90	Neutropenia[b](58) Thrombocytopenia (21) Infection (6)	1	22
		⩽70	50	100	90	78	Neutropenia[b](82) Thrombocytopenia (36) Infection (10)	10	14

CAV, cyclophosphamide, doxorubicin and vincristine; MST, median survival time; NA, not available; ND, no difference; PE, cisplatin and etoposide; PS, performance status; RDI, relative dose intensity; TRD, treatment-related death; TRT, thoracic radiotherapy.

[a] Optimal treatment was defined as four or more treatment cycles.

[b] Grade 4 only.

Table 4 Phase III studies comparing standard and low intensive chemotherapy in elderly or poor risk patients with small cell lung cancer

Authors (year)	Chemotherapy regimen	Number of patients	Age ⩾ 70 (%)	PS ⩾ 2 (%)	RR (%)	Grade 3–4 toxicty (%)	TRD (%)	MST (month)
Girling (1996)[17]	Oral E (50 mg) bid days 1–10	171	Median 67	100	61	Neutropenia[a](14), Infection (4)	14	4.3[b]
	Standard EV or CAV	168	Median 68	100	73	Neutropenia[a] (12), Infection (7)	10	6.1[b]
Souhami et al. (1997)[18]	Oral E (100 mg) bid days 1–5	75	52	48	33	Neutropenia (3), Infection (5)	2	4.8[b]
	Standard CAV/PE	80	44	56	46	Neutropenia (3), Infection (6)	1	5.9[b]
MRC (1996)[19]	EV	156	25	54	55	Leukopenia[a] (4)[b], Stomatitis[c] (34)[b]	1	4.6
	EVMC	154	27	52	54	Leukopenia[a] (16)[b], Stomatitis[c] (54)[b]	7	4.7
James et al. (1996)[20]	Half dose CAV/PE, q11 days	78	Median 63	63	59	Leukopenia (23)[b], Infection (5)	0	6.4
	Standard CAV/PE, q3w	89	Median 63	67	45	Leukopenia (7)[b], Infection (5)	1	5.8
Earl et al. (1991)[21]	Planned CEV	155	Median 65	31	NA	NA	NA	8.2
	Required CEV	145	Median 66	35	NA	NA	NA	6.8

CAV, cyclophosphamide, doxorubicin and vincristine; CEV, cyclophosphamide, etoposide and vincristine; E, etoposide; EV, etoposide and vincristine; EVMC, etoposide, vincristine, methotrexate and cyclophosphamide; MST, median survival time; NA, not available; PE, cisplatin and etoposide; PS, performance status; RR, response rate; TRD, treatment-related death.

[a] Including grade 2–4 toxicity.

[b] Statistically significant.

[c] Including grade 1–4 toxicity.

versus four-drug combinations showed severer toxicity in the four-drug arm with no improvement in survival.[19] A regimen of cisplatin and etoposide (PE) alternating with cyclophosphamide, doxorubicin, and vincristine (CAV) every 10–11 days at half the standard dose failed to reduce toxicity or improve survival compared with the standard PE alternating CAV regimen in a randomized trial.[20] Another randomized trial of cyclophosphamide, etoposide, and vincristine (CEV) given as needed to palliate symptoms, versus CEV given at fixed 3- to 4-week treatment intervals showed that patients randomized to receive chemotherapy as needed had a median interval between cycles of 5 weeks and received only 50% as much total chemotherapy as the patients randomized to the fixed schedule. Although the median survival times were equivalent between both arms, better symptomatic control was achieved with the fixed interval treatment.[21] Thus, these less intensive treatments than the standard treatment are not less toxic or useful for palliation.

The combination of carboplatin and etoposide has been one of the most frequently evaluated regimens in elderly patients with SCLC, and has yielded a response rate of 70–90% and a median survival of 8–10 months for ED and 12–15 months for LD with acceptable toxicity in phase II trials (Table 5).[22,23,25] Modification of the carboplatin dose based on creatinine clearance levels can be especially useful in elderly patients, because many of them have impaired renal function. As a result, this two-drug combination periodically repeated every 3- to 4-weeks has become standard treatment in this patient population (Evidence level, II).

Treatment of elderly patients with limited disease who are in good general condition

A retrospective review of 1208 patients (including 398 SCLC patients, 107 patients more than 70 years of age, 114 patients with PS 2 or higher, and 352 patients with body weight loss greater than 5%) in six EORTC clinical trials (including three for NSCLC, one for SCLC, and two for esophageal cancer) showed that age did not influence the frequency or severity of acute and delayed toxicity of thoracic radiotherapy.[27] Retrospective subset analysis of patients with limited SCLC who were treated with concurrent chemoradiotherapy in phase III trials showed that 80% of the patients 70 years of age or older completed the planned treatment, although hematological toxicity was severer in the elderly group than the younger group (Table 3).[15,16] Only patients with good general condition were included in these trials; 90% had PS 0–1 and 82% had less than 5% body weight loss in the one study,[16] and 84% had PS 0–1 in the other.[15] Thus, the standard chemoradiotherapy can be given to elderly patients in good general condition with PS 0–1, normal organ function and no comorbidity (Evidence level, IV).

Treatment for unselected elderly patients with limited disease

There are three phase II trials of concurrent chemoradiotherapy in this patient population. Although the chemotherapy cycles in these trials were reduced compared with the standard 4–6 cycles, the 5-year survival rates reached to 13–25% with manageable toxicity (Table 6).[28–30] Thus, a combination of full-dose thoracic radiotherapy and two cycles of chemotherapy may be the optimal treatment in unselected elderly patients with limited disease (Evidence level, III).

Discussion

It has been thought to be difficult to establish standard treatments for elderly patients with SCLC, because they form a heterogeneous population in terms of general condition and treatment outcome varies from report to report. However, by classifying studies on the treatment of this population into three types and characterizing subjects included in the studies, relatively consistent results were obtained. To select the optimal treatment for elderly patients, two groups needed to be considered separately: elderly patients in good general condition and all others. The former can be treated with the same strategy as younger patients with minor modifications, if any.

Among elderly patients, 30–50% have PS 2 or higher, and 60–80% have complications in major organs including the kidney, heart, and lung.[6,9–11] They have been treated with oral etoposide or combination chemotherapy at decreased doses or longer intervals. These less intensive treatments than the standard treatment, however, were not less toxic or useful for palliation in the elderly with decreased activity. By contrast, two-drug combination chemotherapy, including a combination of etoposide and carboplatin, produced response rates (RRs) and median survival times (MSTs) comparable to those of younger patients with

Table 5 Phase II trials for elderly or poor risk patients with small cell lung cancer

Authors (year)	Chemotherapy regimen (mg/m^2)	Number of patients	Age $\geqslant 70$ (%)	PS $\geqslant 2$ (%)	RR (%)	Grade 3–4 toxicty (%)	TRD (%)	MST (month)
Evans et al. (1995)[22]	Oral E (100 mg) days 1–7 Carbo (150) day 1	47	Median 69	30	71	Neutropenia (84) Thrombocytopenia (21) Stomatitis (2)	18	LD 14 ED 11
Matsui et al. (1998)[23]	Oral E (40) days 1–14 Carbo[a] day 1	38	100	34	81	Neutropenia (53) Thrombocytopenia (53) Infection (8)	5	LD 15 ED 9
Westeel et al. (1998)[24]	P (30) A (40) V (1) day 1 E (100) days 1, 3, 5	41	100	66	88	Infection (6) Emesis (9)	0	ED 11
Okamoto et al. (1999)[25]	E (100) days 1–3 Carbo[a] day 1	36	100	25	75	Neutropenia (86) Thrombocytopenia (50) Infection (5)	3	LD 12 ED 10
Samantas et al. (1999)[26]	Oral E (100 mg) days 1–12 Carbo (80) weekly	60	Median 66	59	32	Neutropenia (6) Thrombocytopenia (2) Infection (3)	3	5.5

Carbo, carboplatin; E, etoposide; ED, extensive disease; LD, limited disease; MST, median survival time; PAVE, cisplatin, doxorubicin, vincristine and etoposide; PS, performance status; RR, response rate; TRD, treatment-related death.

[a] Dose adjusted for creatinine clearance.

Table 6 Phase II trials of chemoradiotherapy for elderly or poor risk patients with limited small cell lung cancer

Authors (year)	Chemotherapy radiotherapy (Gy/fraction)	Number of patients	Age ⩾70 (%)	PS ⩾2 (%)	RR (%)	Grade 3–4 toxicty (%)	TRD (%)	MST (month)	5-YS (%)
Westeel et al. (1998)[28]	PAVE × 3, PE × 1 20/5, 30/10, 40/15	25	Median 72	28	92	Thrombocytopenia[a] (9) Infection (18) Esophagitis[a] (9)	3	16	24
Murray et al. (1998)[29]	CAV × 1, PE × 1 20/5, 30/10	55	67	45	89	Infection(4)	5	13	18
Jeremic et al. (1998)[30]	Carbo + oral E × 2 45/30 (twice daily)	72	100	17	75	Leukopenia (8) Thrombocytopenia (12) Infection (3) Esophagitis (3)	NA	15	13

CAV, cyclophosphamide, doxorubicin and vincristine; Carbo, carboplatin; E, etoposide; MST, median survival time; NA, not available; PAVE, cisplatin, doxorubicin, vincristine and etoposide; PE, cisplatin and etoposide; PS, performance status; RR, response rate; TRD, treatment-related death; 5-YS, five-year survival rate.

[a] Grade 4 only.

acceptable toxicity in elderly patients. Carboplatin is especially useful for the elderly, because it requires only minimum hydration, its non-hematological toxicity is mild, and the dose can be adjusted according to patient's creatinine clearance. Japanese Clinical Oncology Group (JCOG) evaluated toxicity and efficacy of this method in a phase II study (JCOG9409), and showed that grade 4 neutropenia and thrombocytopenia were noted in 44% and 12% of patients, respectively, and that CR and PR were obtained in 6% and 69%, respectively.[25] We started a large phase III trial in 1997, comparing etoposide (80 mg/m^2 days 1–3) and carboplatin (AUC = 5) with etoposide (the same dose) and cisplatin (25 mg/m^2 days 1–3) in elderly patients with SCLC (JCOG 9702). Up to the present, more than 200 patients were registered in this study.

A recent phase III trial showed that a combination of cisplatin and irinotecan was superior to a combination of cisplatin and etoposide in patients with extensive SCLC, but only patients 70 years of age or younger were included in this study.[31] In addition, there is no clinical trial of irinotecan in elderly patients with SCLC. Another anticancer agent promising in the treatment of SCLC is amrubicin, which yielded a response rate of 79% and median survival time of 11 months in patients with extensive SCLC.[32] Further studies are necessary to evaluate these new agents in the treatment of elderly patients with SCLC.

The chemoradiotherapy used in younger patients may be too intensive for most elderly patients with limited SCLC. One approach that avoids excessive toxicity is to reduce the dose of the chemotherapy or radiotherapy. A recent meta-analysis of chemotherapy alone versus chemotherapy plus radiotherapy in patients with limited SCLC demonstrated survival benefit of radiotherapy added to chemotherapy in patients less than 70 years of age, but the benefit disappeared in the older patients.[33] This finding indicates that the standard treatment in this setting might be chemotherapy alone. The currently available phase II studies of treatment of limited SCLC in the elderly, however, showed that two cycles of chemotherapy plus full-dose radiotherapy produced long-term survivors with acceptable toxicity.[28–30] Thus, which modality should be modified remains controversial, but reduced cycles of chemotherapy combined with full-dose radiotherapy appears to be the treatment of choice at present.

The criteria for the classification of elderly patients into two groups in this review were based on PS, function of major organs, and comorbidity. However, they may be inadequate to evaluate this heterogeneous elderly population. In future clinical trials, it will be important to evaluate the influence of cancer treatment on the functional status of the elderly. A comprehensive geriatric assessment designed to improve the health care of elderly people consists mainly of instruments for evaluating activities of daily living, physical function, cognitive function, and emotional status.[34, 35] It has been used as a diagnostic tool to screen for problems and to determine the needs of the geriatric population for in-home assistance, home-health service, or hospital care, but it may be also useful for our purpose.

In conclusion, although the evidence levels based on clinical trials currently available are low, it is possible to select the optimal treatment for elderly patients with SCLC by dividing them into patients in good and poor general condition.

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Short Communication

Phase I study of cisplatin analogue nedaplatin (254-S) and paclitaxel in patients with unresectable squamous cell carcinoma

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The recommended phase II dose of paclitaxel 180 mg m^{-2} given as a 3-h infusion followed by nedaplatin 100 mg m^{-2} in a 1-h infusion every 3–4 weeks was determined in 52 chemo-naive patients with unresectable squamous cell carcinoma (SCC), with a promising response rate for lung SCC of 55%.

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Squamous cell carcinoma (SCC) arises from the epithelial tissue of many different organs. Although localised diseases can be treated using surgical resection or curative radiotherapy, advanced SCC continues to have a poor prognosis and the standard treatment has not been established (DeVita *et al*, 2001). Cisplatin-based chemotherapy has been used for the treatment of advanced SCC, regardless of the site of tumour origin (DeVita *et al*, 2001).

Nedaplatin (cis-diammine-glycolate-*O,O'*-platinum II, 254-S) is a second-generation platinum derivative that has an antitumour activity comparable to that of cisplatin (Kobayashi *et al*, 1991) but is less toxic to the kidney (Kameyama *et al*, 1990), as seen in preclinical experiments. Nedaplatin produced promising response rates in phase II trials for the treatment of SCC arising from the head and neck (Inuyama *et al*, 1992), lung (Yamamoto *et al*, 2000), oesophagus (Taguchi *et al*, 1992), and uterine cervix (Noda *et al*, 1992). Paclitaxel is another promising drug for the treatment of advanced SCC, as shown by the favourable response rates obtained in phase II trials for head and neck (Forastiere *et al*, 1998), non-small-cell lung (Sekine *et al*, 1996), oesophageal (Ajani *et al*, 1994), and cervical (McGuire *et al*, 1996) cancers.

A combination of nedaplatin and paclitaxel is a promising chemotherapeutic regimen because a significant synergistic effect was obtained for this combination in a preclinical mice tumour model (Yamada *et al*, 2001), and the combination of platinum compounds and paclitaxel is one of many standard regimens (Schiller *et al*, 2002). The objectives of this phase I trial were (1) to evaluate the toxicity of the regimen and to determine the maximum tolerated dose (MTD) and recommended phase II dose (RPTD) of nedaplatin and paclitaxel, and (2) to observe the antitumour effects of this regimen on SCC arising in various organs.

PATIENTS AND METHODS

Patient selection

The eligibility criteria for enrolment in the trial were as follows: histologically or cytologically proven SCC; unresectable disease; measurable disease; no previous chemotherapy; age between 20 and 75 years; performance status of 0 or 1 (Oken *et al*, 1982); adequate bone marrow function (white blood cell (WBC) count $\geqslant 4.0 \times 10^9 l^{-1}$, neutrophil count $\geqslant 2.0 \times 10^9 l^{-1}$, haemoglobin $\geqslant 10.0$ g dl^{-1} and platelet count $\geqslant 100 \times 10^9 l^{-1}$), liver function (total bilirubin $\leqslant 1.5$ mg dl^{-1} and transaminase $\leqslant 100$ IU l^{-1}), and renal function (serum creatinine $\leqslant 1.5$ mg dl^{-1} and creatinine clearance $\geqslant 60$ ml min^{-1}); and a PaO_2 $\geqslant 60$ Torr. Patients were excluded from the trial for any of the following reasons: uncontrolled malignant pleural or pericardial effusion; a concomitant serious illness contraindicating chemotherapy; pregnancy; or breast-feeding. All patients gave their written informed consent.

Treatment schedule

The levels and respective doses of paclitaxel (mg m^{-2}) and nedaplatin (mg m^{-2}) are shown in Table 1. Paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication as previously described (Sekine *et al*, 1996). Normal saline (500 ml) and granisetron (40 μg kg^{-1}) in 100 ml of normal saline were given intravenously, followed by nedaplatin diluted in 250 ml of normal saline administered in a 1-h intravenous infusion. This treatment was repeated every 3–4 weeks.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed at least once a week throughout the course of treatment. If grade 4 neutropenia was noted, the neutrophil count was repeated 4 days later to determine whether the grade 4 neutropenia had lasted for 5 days or longer. Acute toxicity was graded according to the NCI Common Toxicity Criteria, version 2.0, issued in 1998 (JCOG, 1998). Subsequent cycles of chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $\leqslant 3.0 \times 10^9 l^{-1}$, neutrophil count $\leqslant 1.5 \times 10^9 l^{-1}$, platelet count $\leqslant 100 \times 10^9 l^{-1}$, serum creatinine level $\geqslant 1.6$ mg dl^{-1}, grade 2 elevated hepatic transaminase level or total serum bilirubin, fever $\geqslant 38$°C, or a performance status $\geqslant 2$.

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Table 1 Dose level and number of patients accrued

Level	Paclitaxel ($mg\,m^{-2}$)	Nedaplatin ($mg\,m^{-2}$)	No. of patients: Accrued	Evaluable for DLT[a]	Developing DLT[a]
1	135	60	6	6	2
2	150	60	3	3	0
3	150	80	3	3	0
4	180	80	7	6	1
5	180	100	12	12	4
6	210	100	21	19	8

[a]Dose-limiting toxicity.

The treatment was terminated if the above-mentioned toxicity did not disappear in 3 weeks. If grade 4 leukopenia, grade 4 neutropenia for 5 days or longer, grade 3–4 febrile neutropenia, or grade 3–4 neutropenia with infection was noted, $50\,mg\,m^{-2}$ of granulocyte colony-stimulating factor (G-CSF) was given subcutaneously, and the doses of paclitaxel and nedaplatin were reduced by 25% in subsequent chemotherapy cycles.

Dose-limiting toxicity, MTD, and RPTD

The dose-limiting toxicity (DLT) was defined as grade 4 neutropenia lasting 5 days or longer, grade 3–4 febrile neutropenia, grade 3–4 neutropenia with infection, grade 4 leukopenia, a platelet count $<20 \times 10^9\,l^{-1}$, and grade 3 or greater nonhaematological toxicity other than nausea and vomiting. Doses were escalated according to the frequency of DLT evaluated during the first cycle of chemotherapy. Three patients were initially enrolled at each dose level. If none of the patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If one of the three patients experienced DLT, then three additional patients were enrolled at the same dose level, bringing the total to six patients for that dose level. If two or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. If two or all the initial three patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD. Six to 15 additional patients were enrolled at the RPTD to confirm that the frequency of DLT was less than one-third.

Response evaluation

The objective tumour response was evaluated according to the WHO criteria issued in 1979 (WHO, 1979).

Study design, data management, and statistical considerations

The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center, Tokyo Japan. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 12 months were planned. The overall survival time was estimated using the Kaplan–Meier method (Armitage and Berry, 1994). Survival time was measured from the date of study registration until the date of death from any cause.

RESULTS

Patient characteristics

Between August 1999 and December 2002, 53 patients were registered in the study. One patient at level 5 developed a bone fracture prior to treatment and did not receive chemotherapy. This patient was excluded from all the analyses. Of the remaining 52 patients (42 males and 10 females) with a median age of 62 years (range 49–75), 42 (81%) patients had lung SCC, followed by thymic SCC in five patients and head and neck SCC in four patients. Of the 52 patients, 24 and 24 had metastatic and locally advanced diseases, respectively.

Treatment delivery, toxicity, MTD, and RPTD

Treatment delivery was summarised in Table 2. Severe toxicity was mainly manifested as leucopenia, neutropenia, and associated infection, but the frequency of these symptoms did not differ between dose levels (Table 3). Grade 3 anaemia and thrombocytopenia were only noted in one patient (5%) each; both these patients had been treated at dose level 6. No grade 3–4 nausea, neuropathy, or myalgia was noted. A grade 3–4 elevation in creatinine, grade 3–4 hyponatremia, appetite loss, and diarrhoea were only observed at level 6. One patient treated at level 6

Table 2 Treatment delivery

	No. of patients (%): Levels 1–4 ($n=19$)	Level 5 ($n=12$)	Level 6 ($n=21$)
Chemotherapy cycles			
5	1 (5)	0 (0)	0 (0)
4	7 (37)	4 (33)	5 (24)
3	2 (11)	2 (17)	3 (14)
2	5 (26)	4 (33)	8 (38)
1	4 (21)	2 (17)	5 (24)
Median	3	3	2
Dose reduction in subsequent cycles			
None	12 (63)	9 (75)	12 (50)
Required	3 (16)	1 (8)	4 (19)
Not administered	4 (21)	2 (17)	5 (24)

Table 3 Toxicity in all courses

	Levels 1–4 ($n=19$)			Level 5 ($n=12$)			Level 6 ($n=21$)		
	3	4	3–4 (%)	3	4	3–4 (%)	3	4	3–4 (%)
Leukopenia	6	0	(32)	5	0	(42)	6	1	(33)
Neutropenia	3	10	(68)	2	9	(92)	3	12	(71)
Anaemia	0	0	(0)	0	0	(0)	1	0	(5)
Thrombocytopenia	0	0	(0)	0	0	(0)	1	0	(5)
AST	0	0	(0)	0	0	(0)	1	0	(5)
ALT	0	0	(0)	1	0	(8)	0	1	(5)
Creatinine	0	0	(0)	0	0	(0)	0	1	(5)
Hyponatremia	0	0	(0)	0	0	(0)	2	1	(14)
Infection	4	0	(21)	4	0	(33)	6	0	(29)
Appetite loss	0	0	(0)	0	0	(0)	1	0	(5)
Diarrhoea	0	0	(0)	0	0	(0)	2	0	(10)
Constipation	0	0	(0)	0	0	(0)	0	1	(5)
Arrhythmia	2	0	(11)	0	0	(0)	0	0	(0)
Lung toxicity	0	0	(0)	0	0	(0)	2	0	(10)

developed grade 2 leukopenia, fever, watery diarrhoea, and grade 4 ileus, but recovered in 5 days. Two patients at level 6 developed grade 3 interstitial pneumonitis, but quickly recovered with oxygen therapy alone in one patient and with oxygen and steroid therapy in the other patient. No treatment-related deaths occurred in the study.

In all, 19 DLTs were noted in 15 patients. Of the 1nine DLTs, 13 were neutropenic fever or documented infection and six were nonhaematological. At level 6, only two of the first six patients developed DLT; therefore, 15 additional patients were entered at this level to confirm the frequency of DLT. Two patients were excluded from the DLT analysis because G-CSF was administered before the duration of grade 4 neutropenia had been determined (protocol violation). Of the remaining 13 patients, six developed DLT. Thus, eight (42%) of the 19 patients evaluated for DLT developed DLT at level 6; this dose level was therefore determined to be the MTD. An additional six patients were registered at level 5, and four (33%) of the 12 patients at level 5 developed DLT; this level was determined to be the RPTD.

Objective responses and survival

Of the 42 patients with lung SCC, two CRs and 21 PRs were noted, and the overall response rate (95% confidence interval) was 55% (39–70%). No difference in the response rates for levels 1–4 and levels 5–6 were observed. One PR was noted in a patient with thymic SCC, and one PR was noted in a patient with head and neck SCC. The overall survival time (95% confidence interval) in all patients ($n = 52$) was 11.1 (6.4–15.8) months.

DISCUSSION

This study showed that the combination of nedaplatin and paclitaxel was feasible with acceptable toxicity, and that the RPTD of nedaplatin was 100 mg m^{-2} over 1 hour, which is the full dose of this agent, while that of paclitaxel was 180 mg m^{-2} over 3 h. These doses are comparable to doses for practical use and those determined by previous phase I trials of cisplatin or carboplatin in combination with paclitaxel, where 180–225 mg m^{-2} of paclitaxel was given with the full dose of platinum-agent (Akiyama *et al*, 2001; Kurata *et al*, 2001). The toxicity profile in the present study was similar to that of the carboplatin and paclitaxel combination (Akiyama *et al*, 2001).

The primary objectives of phase I trials are to evaluate toxicity and to establish a recommended drug dose for a given administration schedule; an additional goal of these trials is to look for evidence of the drug's antitumour activity. Objective tumour responses to newly investigated drugs are a promising clue for determining specific tumour types for subsequent phase II trials; therefore, patients with various tumours are usually registered in phase I trials (Sekine *et al*, 2002). In cases where some information on the antitumour activity of a drug is available, patients can be selected so that the chance of a response is maximised. This study was a histology-oriented phase I trial, and objective tumour responses were observed in about half of the patients.

The combination of nedaplatin and paclitaxel is particularly promising for the treatment of patients with lung SCC, as shown by the high response rate of 55%. Adenocarcinoma, large-cell carcinoma, adenosquamous carcinoma, and SCC of the lung have been grouped together as non-small-cell lung cancer because treatment response and prognosis are similar for these histologies. A recent cDNA microarray analysis of non-small-cell lung cancer tissue, however, showed that the gene expression profiles of SCC and adenocarcinoma are different (Kikuchi *et al*, 2003), and these differences may lead to different responses to anticancer agents, including nedaplatin. Thus, optimal chemotherapy regimens for the treatment of non-small-cell lung cancer should be established according to each tumour's histology. The numbers of patients with head and neck SCC and patients with thymic SCC were too small to comment on the antitumour effects of this regimen.

In conclusion, the combination of nedaplatin and paclitaxel is a feasible treatment, and the RPTD is paclitaxel 180 mg m^{-2} given as a 3-h infusion followed by nedaplatin 100 mg m^{-2} in a 1-h infusion every 3–4 weeks. This regimen was highly effective for the treatment of untreated lung SCC.

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