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ORIGINAL ARTICLE

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Retrospective comparison of toxicity and efficacy in phase II trials of 3-h infusions of paclitaxel for patients 70 years of age or older and patients under 70 years of age

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Abstract *Purpose*: To evaluate the safety and efficacy of paclitaxel in elderly patients with advanced non-small-cell lung cancer (NSCLC). *Methods*: We compared the toxicity, response, survival and pharmacokinetic parameters between patients between 70 and 75 years of age (elderly group) and those under 70 years of age (younger group) who were enrolled in two phase II trials of 3-h infusions of paclitaxel. *Results*: A total of 120 patients were eligible for the studies, of whom 28 were in the elderly group and 92 in the younger group. Neutropenia was the most prominent toxicity. Grade 3–4 neutropenia was recorded in 89.3% of the elderly group and in 73.9% of the younger group ($P = 0.13$). Other hematological and non-hematological toxicities were mild regardless of age. Tumor response (46.4% vs 32.2%) and median survival time (9.8 months vs 6.8 months) did not differ between the elderly and younger groups. Pharmacokinetic studies failed to detect any difference between the two groups. *Conclusion*: Intravenous 3-h infusions of paclitaxel are as safe and effective in elderly patients with NSCLC as in younger patients.

Key words Paclitaxel · Non-small-cell lung cancer · Elderly · Chemotherapy

Introduction

Since the population of elderly patients with non-small-cell lung cancer (NSCLC) is increasing in Japan as well as in Western countries, the treatment for these patients is one of the current and most important issues for medical oncologists. However, the safety of commonly used chemotherapy against NSCLC has not been fully analyzed in elderly patients [1].

Paclitaxel, which shifts the equilibrium toward microtubule assembly and stabilizes microtubules by preventing depolymerization, is a promising drug in the treatment of various solid tumors [2]. This drug is active in NSCLC with a response rate of about 10–38% and a median survival time of about 19–45 weeks [3, 4, 5, 6, 7]. However, the safety and efficacy of paclitaxel in the elderly have not been evaluated. To estimate the influence of aging, we reanalyzed the clinical outcomes and pharmacokinetics of paclitaxel administered over 3 h.

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Materials and methods

Two phase II trials of paclitaxel, both of which had the same eligibility criteria and regimen, were performed by two Japanese groups from March 1994 to November 1994 [6, 7]. We analyzed the results of these two trials and compared the toxicity, tumor response and survival between patients 70 years of age or more and those less than 70 years of age.

Patients with histologically or cytologically proven unresectable stage III or IV NSCLC who had received no prior chemotherapy or radiotherapy for the primary lesion were eligible for these studies. They were required to meet the following criteria: to be between 15 and 75 years old; to have a performance status of 0 to 2; a life expectancy of 3 months or more; measurable lesions; and adequate organ functions as indicated by a leukocyte count $>4000/\mu l$, a neutrophil count $>2000/\mu l$, a platelet count $>100{,}000/\mu l$, a serum bilirubin level <1.5 mg/dl, a serum creatinine level <1.5 mg/dl and a normal electrocardiogram. Patients who had symptomatic brain metastasis, active multiple malignancies, acute inflammatory disease and a history of severe hypersensitivity reaction were excluded. Written informed consent was obtained from all patients.

Patients were treated with 210 mg/m^2 paclitaxel as a 3-h intravenous infusion every 3 weeks. Premedication consisted of 20 mg dexamethasone (14 h and 7 h before paclitaxel), 50 mg ranitidine, and 50 mg diphenhydramine (30 min before paclitaxel).

Toxicity and tumor response were graded according to the World Health Organization (WHO) criteria [8]. In addition, adverse effects such as peripheral edema, hypotension, and central

Table 1 Patients characteristics

	Age <70 years (n = 92)		Age ≥70 years (n = 28)	
	Number	%	Number	%
Sex				
Male	71	77.2	23	82.1
Female	21	22.8	5	17.9
Performance status				
0–1	83	90.2	23	82.1
2	9	9.8	5	17.9
Histological type				
Squamous cell carcinoma	20	21.7	15	53.6
Adenocarcinoma	61	66.3	11	39.3
Large-cell carcinoma	7	7.6	2	7.1
Adenosquamous carcinoma	4	4.3	0	
Stage				
IIIA	4	4.3	5	17.9
IIIB	18	19.6	6	21.4
IV	70	76.1	17	60.7

nervous system symptoms, were evaluated using the Southwest Oncology Group (SWOG) criteria [9] because the WHO criteria does not include such effects.

Plasma samples for the pharmacokinetic evaluation of paclitaxel were collected from 14 patients. Heparinized blood samples were obtained before infusion, at 1.5 h during infusion, at the end of infusion, and at 5, 15 and 30 min, and 1, 2, 3, 4, 6, 12, 24 and 48 h after infusion. Plasma paclitaxel concentrations were measured by a high-performance liquid chromatographic assay using *n*-hexy *p*-hydroxy benzonate as an internal standard. The following pharmacokinetic parameters were obtained: area under the concentration versus time curve (AUC), maximum plasma concentration (C_{max}), half-life ($T_{1/2}$), mean residence time (MRT), total clearance (CL), and the duration of the paclitaxel concentration above 0.1 μM ($D > 0.1\ \mu M$).

The survival period was measured from the start of treatment until death or the last follow-up. Survival curves were estimated by the Kaplan-Meier method, and the log-rank test was used to compare two survival distributions. The chi-square test was used to compare pretreatment characteristics, response rates, and incidence of severe toxicity. The significance level (P-value) was set at 0.05.

Results

Of a total of 122 patients who entered the two studies, 2 were excluded from this analysis. One patient was found to have pulmonary metastasis from colon cancer and did not receive paclitaxel, and the other died of pneumonia before paclitaxel was administered. Thus, included in the current study were 120 patients, 28 aged 70 years or more (elderly group) and 92 aged less than 70 years (younger group). There was no difference in patient characteristics between the two age groups (Tables 1 and 2).

A total of 352 cycles of paclitaxel were administered to the 120 patients with a median number of three cycles (range on to five) in the elderly group and three cycles (range one to nine) in the younger group (Table 3). The most prominent toxicity was neutropenia. Grade 3–4 neutropenia was recorded in 89.3% of the elderly group and in 73.9% of the younger group, with no statistically significant difference between the groups ($P = 0.13$).

Table 2 Underlying disease

	Age <70 years (n = 92)		Age ≥70 years (n = 28)	
	Number	%	Number	%
No	62	67.4	18	64.3
Yes	30	32.6	10	35.7
Pulmonary emphysema	2	2.2	3	10.7
Pulmonary fibrosis	2	2.2	1	3.6
Bronchial asthma	0		2	7.1
Lung asbestosis	1	1.1	0	
Hypertension	11	12.0	4	14.3
Angina pectoris	1	1.1	0	
Aortic valve stenosis	1	1.1	0	
Arteriosclerotic obliteration	1	1.1	0	
Diabetes mellitus	6	6.5	2	7.1
Gout	4	4.3	0	
Hepatitis	4	4.3	0	
Glaucoma	1	1.1	0	

Table 3 Actual delivery of paclitaxel

Cycles	Age <70 years (n = 92)		Age ≥70 years (n = 28)	
	Number	%	Number	%
1	9	9.8	5	17.9
2	19	20.7	6	21.4
3	41	44.6	10	35.7
4	12	13.0	4	14.3
5+	11	12.0	3	10.7

Grade 3–4 leukopenia was observed in 25.0% of the elderly group and in 28.3% of the younger group, but grade 3–4 thrombocytepenia was not noted in either group. Grade 3 to 4 elevation of blood urea nitrogen (BUN) was noted in 10.7% of the elderly group, but this was not associated with an elevated creatinine level. There was no difference in the frequency of other non-hematological toxicities (Table 4). No toxic death occurred in either group.

Table 4 Toxicity noted in the two age groups

	Age < 70 years (n = 92)				Age ≥70 years (n = 28)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	Number	%	Number	%	Number	%	Number	%
Anemia	5	5.4	0		1	3.6	0	
Leukocytopenia	23	25.0	3	3.3	6	21.4	1	3.6
Neutropenia	26	28.3	42	45.7	10	35.7	15	53.6
Thrombocytopenia	0		0		0		0	
Elevation of BUN	0		0		2	7.1	1	3.6
Elevation of GOT	1	1.1	0		0		0	
Nausea/vomiting	3	3.3	0		3	10.7	0	
Pulmonary toxicity	1	1.1	0		1	3.6	1	3.6
Allergic reaction	1	1.1	0		0		0	
Peripheral edema	0		0		1	3.6	0	
ST-T change	0		0		1	3.6	0	
Hypotension	1	1.1	0		0		0	
Central nerve toxicity	1	1.1	0		0		0	
Peripheral neuropathy	2	2.2	0		0		0	
Myalgia	4	4.3	0		0		0	
Arthralgia	4	4.3	0		0		0	

In 118 patients evaluable for tumor response, 1 complete response and 41 partial responses were noted, resulting in a total response rate of 35.6%. Age did not influence the response rate (Table 5). Of the 120 patients, 114 (95%) had died by the time of this analysis and the rest were still alive. The median survival time in the elderly group and younger group was 9.8 months and 6.8 months, respectively ($P = 0.10$). The 1-year survival rate was 37.1% in the elderly group and 28.3% for the younger group (Fig. 1).

The mean pharmacokinetic data are summarized in Table 6. The elderly group comprised 3 patients and the younger group 11 patients. There was no difference between the two groups.

Discussion

There are few data on toxicity and efficacy of chemotherapy in patients of 70 years of age or older with advanced NSCLC. This study showed that paclitaxel is safe and efficacious against NSCLC in elderly patients as well as in younger patients.

The physiological hematopoietic capacity may be affected by aging, which may lead to an increased susceptibility to cytotoxic therapy [10]. It has been confirmed by studies using magnetic resonance imaging (MRI) and histological sections that the amount of hematopoietic tissue in the bone marrow decreases and fatty bone marrow increases with age [11, 12, 13]. However, in this analysis, the hematological toxicities in the older group were as severe as in the younger group. This may be because single-agent chemotherapy with paclitaxel has a relatively low dose intensity when compared with combination chemotherapy. We also failed to detect any differences in non-hematological toxicity between the two groups. However, we should consider the possibility of having overlooked central neurotoxicity such as dementia, dysarthria, ataxia and incoordination, because it is difficult to estimate retrospectively these toxicities which are relatively common in elderly patients but rare in the majority of younger patients.

We failed to find any differences in the pharmacokinetic parameters between the older and younger groups.

Table 5 Tumor responses by the age group

Response	Stage III disease		Stage IV disease	
	Age < 70 years (n = 22)	Age ≥70 years (n = 11)	Age < 70 years (n = 70)	Age ≥70 years (n = 17)
Complete response	1	0	0	0
Partial response	6	6	22	7
No change	11	5	31	6
Progressive disease	4	0	15	4
Non-evaluable	0	0	2	0
Response rate (%)	31.8	54.5	32.4	41.2

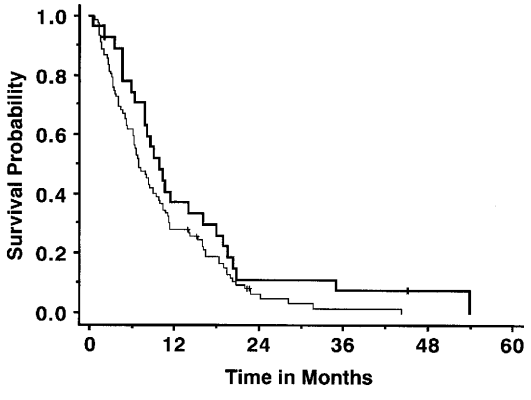

Fig. 1 Overall survival of patients aged 70 years or more (*thick line*), and patients aged less than 70 years (*thin line*). There was no significant difference in survival between the two age groups ($P = 0.10$)

Table 6 Mean pharmacokinetic parameters of paclitaxel administered as a 3-h infusion (C_{max} maximum plasma concentration, AUC area under the concentration versus time curve, MRT mean residence time, $T_{1/2}$ half-life, CL total clearance, $D > 0.1\ \mu M$ duration of paclitaxel concentration above 0.1 μM)

Age (years)	n	C_{max} (μg/ml)	AUC (μg · h/ml)	MRT (h)	$T_{1/2}$ (h)	CL (ml/min/m^2)	D > 0.1 μM (h)
≥70	3	6.28	21.5	7.57	14.3	168	22.2
< 70	11	6.80	21.6	7.01	12.5	162	22.0

Paclitaxel is metabolized in the liver by the cytochrome P450 system, mainly the P450 3A4 enzyme [14, 15]. The frequency of the CYP3A4 variant allele has been estimated to be 53% in African Americans, 9% in Caucasian Americans, 0% in Taiwanese, and 0% in Japanese, although the variant allele does not seem to be strongly related to CYP3A4 activity [16, 17]. The association between age and P450 enzyme activity is controversial. Although studies on cytochrome P450 in human liver biopsy specimens have shown no significant association between monooxygenase activity and the age of the patient [18, 19], the liver clearance of antipyrine, which constitutes a sensitive indicator of hepatic microsomal enzyme activity, is reduced in the elderly [20, 21]. Thus, the activity of drug metabolism in the liver probably varies between drugs in the elderly.

Aging affects the prognosis of some kinds of malignancies. For example, hematological malignancies are associated with a poor prognosis in older people [22, 23, 24]. An association between increased p-glycoprotein expression and a poor complete remission rate has been demonstrated in elderly patients with acute myeloid leukemia [25, 26]. This may be explained by the fact that intensive chemotherapy appears to have an unacceptable level of toxicity in the elderly, and such patients tend to receive chemotherapy at lower doses [27, 28]. In this study, however, we could not detect a difference in the response and survival rates between the two groups. Therefore, the efficacy of chemotherapy seems not to be affected by aging in patients with NSCLC when they are 75 years of age or less.

In conclusion, 3-h intravenous infusions of paclitaxel were tolerable for patients of up to 75 years of age if they had a good performance status and adequate organ function, and were as effective for NSCLC in elderly patients as in younger patients.

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