Table 4 Phase I trials for elderly patients with advanced non-small cell lung cancer

Author	Study period	Form of report	Country	Chemotherapy regimen (MTD)	No. of assessable pts	Eligibility criteria regarding age (years)	Main dose-limiting toxicity	No. of pts with early death (%)	RR (%)	Ref.
Inoue	2000–2001	F	Japan	DOC 30 mg/m^2 d1,8,15 q4w	11	>69	Neutropenia, diarrhea	0	18	[78]
Yamamoto	NR	A	Japan	254-S 100 mg/m^2 d1,8,15	36	>69	Neutropenia	NR	33	[79]
Ohe	1998–1999	F	Japan	CDDP 25 mg/m^2 d1,8,15 q4w DOC 25 mg/m^2 d1,8,15	12	>74	Infection	0	58	[80]

Abbreviations: MTD: maximum-tolerated dose; pts: patients; RR: response rate; ref.: references; F: full text; A: abstract only; DOC: docetaxel; 254-S: nedaplatin; CDDP: cisplatin; DOC: docetaxel; NR: not recorded.

Table 5 Characteristics of patients enrolled in elderly-specific clinical trials

Author	Study Period	Chemotherapy regimen	No. of assessable pts	Median age (range) (years)	%Female	%PS 0/1	%Ad	%Stage IV	%Comorbidities	Ref.
ELVIS	1996–1997	VNR	76	74 (70–85)	15	76	34	74	49	[33]
		BSC	78	74 (70–86)	12	76	38	72	65	
Frasci	1997–1999	VNR	60	74 (71–81)	8	78	40	58	25	[34]
		VNR	60	75 (71–83)	12	73	38	60	23	
		GEM								
Gridelli	1997–2000	VNR	233	74 (63–83)	12	81	35	71	90	[35]
		GEM	233	74 (70–86)	17	82	33	70	89	
		VNR	232	74 (69–84)	21	81	33	69	87	
		GEM								
Marinis	1990–1992	VDS	30	75 (65–88)	15	65	NR	40	NR	[36]
		LND	32							
		VDS	33							
		LND								
		BSC	31							
Colleoni	1992–1994	VNR	25	70 (65–80)	20	64	76	68	NR	[37]
Veronesi	1992–1994	VNR	23	72 (70–80)	4	NR[a]	35	48	NR	[38]
Tononi	1993–1996	VNR	25	71 (65–77)	16	NR[b]	60	52	NR	[39]
Gridelli	1994–1995	VNR	43	73 (70–80)	12	49	26	56	65	[40]
Buccheri	1995–1998	VNR	40	75 (70–83)	13	23	50	45	NR	[41]
Mattioli	1996–	VNR	15	70 (65–84)	7	NR	NR	53	100	[42]
Schulz	NR	VNR[c]	58	73 (65–87)	NR	88	NR	NR	NR	[43]
Gridelli	2001–2002	VNR[c]	56	74 (70–82)	25	52	NR	77	88	[44]
Quoix	NR	GEM(q4w)	42	75 (71–90)	14	81	29	62	NR	[45]
		GEM(q3w)	39	75 (70–89)	21	72	39	72		
Bianco	1996–1999	GEM	52	70 (65–82)	21	85	29	19	60	[46]
Ricci	1997–1998	GEM	46	75 (70–81)	11	80	48	65	NR	[47]
Altavilla	1997–1998	GEM	21	74 (70–81)	14	52	33	67	NR	[48]
Martoni	1997–1999	GEM	46	73 (70–82)	17	NR[b]	43	39	52	[49]
Wilson	NR	GEM	35	74 (66–89)	41	NR	65	73	NR	[50]
Pasquini	NR	GEM	22	NR	NR	NR	NR	NR	NR	[51]
Yoshimura	1997–1999	DOC	30	76 (70–83)	27	70	53	73	NR	[52]
Tibaldi	NR	DOC	17	73 (70–80)	18	18	29	NR	NR	[53]
Fidias	1998–2000	PTX	35	76 (70–85)	32	80	71	86	NR	[54]
Gallotti	1990–1992	VDS	22	72 (64–74)	NR	0	NR	NR	NR	[55]
Baldini	NR	DXF	33	74 (70–80)	9	84	52	67	NR	[56]

Table 5 *(Continued)*

Author	Study Period	Chemotherapy regimen	No. of assessable pts	Median age (range) (years)	%Female	%PS 0/1	%Ad	%Stage IV	%Comorbidities	Ref.
Martins	1996–1998	CDDP + VNR	44	74 (71–85)	NR	50	NR	43	NR	[57]
Lippe	1999–2000	CDDP + VNR	13	70 (65–80)	23	69	NR	92	NR	[58]
Feliu	1999–	CDDP + GEM	46	74 (70–81)	9	65	24	57	74	[59]
Lippe	NR	CDDP + GEM	29	70 (66–77)	7	86	41	55	NR	[60]
Berardi	NR	CDDP + GEM	48	74 (70–78)	23	50	44	69	NR	[61]
Moscetti	2000–	CDDP + GEM	34	71 (65–77)	NR	82	47	50	NR	[62]
Niho	2000–2002	CDDP + DOC	33	77 (75–86)	21	100	61	52	NR	[63]
Kanat	NR	CDDP + ETP	24	72 (70–77)	8	38	21	71	NR	[64]
Souquet	1995–	CDDP + IFO + MMC	16	NR	NR	NR	NR	NR	NR	[65]
LeCaer	NR	CBDCA + VNR	40	72 (70–82)	23	100	30	80	NR	[66]
Maestu	1998–2000	CBDCA + GEM	79	74 (65–81)	NR	67	17	53	62	[67]
Molinier	2002–	CBDCA + PTX	43	74 (70–88)	26	89	58	84	NR	[68]
Jatoi	2000–2001	CBDCA + PTX	49	73 (65–85)	41	77	NR	86	NR	[69]
Gridelli	NR	CBDCA + ETP	14	73 (70–77)	7	71	36	64	43	[70]
Cuzzoni	NR	CBDCA + ETP	42	68 (65–75)	29	NR[b]	83	57	NR	[71]

Santomaggio	2000 onwards	GEM + VNR GEM + VDS	30 29	75	NR	49	NR	42	NR	[72]
Maestu	2001–2003	GEM VNR	43	74 (70–82)	NR	56	NR	65	79	[73]
Baron	1999–1999	GEM VNR	40	75 (70–84)	20	73	NR	43	NR	[74]
Chen	1998–2001	GEM VNR	40	83 (80–88)	20	20	50	50	100	[75]
Salvati	1990–1991	LND CPA	35	73 (71–79)	9	100	34	19	NR	[76]
Malarme	NR	IFO VDS	20	72 (66–79)	20	NR	NR	75	NR	[77]
Inoue	2000–2001	DOC	11	73 (70–78)	18	100	55	27	NR	[78]
Yamamoto	NR	254-S	36	76 (70–82)	11	97	NR	58	NR	[79]
Ohe	1998–1999	CDDP DOC	12	76 (75–80)	8	100	6	67	NR	[80]

Abbreviations: pts: patients; PS: performance status; Ad: adenocarcinoma; ref.: references; ELVIS: The Elderly Lung Cancer Vinorelbine Italian Study Group; VNR: vinorelbine; GEM: gemcitabine; VDS: vindesine; LND: lonidamine; DOC: docetaxel; PTX: paclitaxel; DXF: doxifluridine; CDDP: cisplatin; IFO: ifosphamide; MMC: mitomycin C; CBDCA: carboplatin; ETP: etoposide; CPA: cyclophosphamide; 254-S: nedaplatin; NR: not recorded.

[a] Median performance status was 1 (range, 0–3).

[b] Median performance status was 1 (range, 0–2).

[c] Oral vinorelbine. Median performance status was 2 (range, 1–3).

[52–54]. The efficacy of these agents appeared to be comparable with that of vinorelbine or gemcitabine.

Regarding combination chemotherapy regimens, platinum-based chemotherapy was performed in 16 trials, with a response rate ranging from 0 to 58% and a median survival time ranging from 27 to 74 weeks. The efficacy of non-platinum combination regimens was evaluated in nine trials, including six reports examining gemcitabine plus vinorelbine in a total of 425 patients [34,35,72–75]. The response rates and median survival times ranged from 3 to 65% and from 17 to 43 weeks, respectively. The efficacy of multidrug chemotherapy seemed to be comparable with that of single-agent chemotherapy, a finding that was confirmed in one phase III trial [35].

Quality-of-life was used in 10 trials (21%) as one of the endpoints. Of note, systemic chemotherapy improved the quality-of-life in the majority of the trials. In particular, the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) phase III trial evaluated quality-of-life as the primary endpoint and clearly demonstrated that vinorelbine improved not only overall survival, but also quality-of-life, when compared with best supportive care alone [33].

4. Discussion

Most trials identified in this study included only a small number of patients, and a statistically accurate estimation of the required sample size was often lacking. Of the 48 trials, the sample size was properly calculated in only 16 trials (33%). In addition, since several trials were reported only as an abstract, the details of the trials were difficult to obtain. Such missing data made some information unreliable, resulting in a limitation of the current study.

The term "elderly patient" was simply defined based on calendar age in all the trials, and an arbitrary age of 70 or 65 years was frequently used as the cut-off value. Aging is a very individualized process that involves changes in physical, cognitive, emotional, social and economic domains and these changes in an individual person cannot be predicted by only one's calendar age. Recently, several reports remarked on the issue of comprehensive geriatric assessment (CGA) and the possibility to include such instrument in study designs for elderly patients [83]. Although CGA has not been standardized, several screening tests were proposed for CGA, assessing mental status, emotional status, depression, activities of daily living, instrumental activities of daily living, home environment, social support, comorbidity, nutrition, and polypharmacy.

Our study revealed that only 27% of the authors reported comorbid conditions, indicating that physicians seldom recognize their importance. Frasci et al. demonstrated in a phase III trial that a high Charlson comorbidity score was strongly associated with a high risk of early treatment suspension [34]. Comorbidity is also reported to be a prognostic factor for overall survival [84,85] and the number of comorbidities increases with advancing age in cancer patients [2]. Thus, the assessment of comorbid status is one of the important issues especially in clinical trials of elderly patients.

The median prevalence of comorbidity in the trials we analyzed was at most 65%, whereas community-based studies have shown that approximately 80% of elderly cancer patients have one or more comorbidity [2,85,86]. This difference might not be attributed to exclusion of patients with a performance status of 3 or 4 in most trials we identified, since comorbidity and performance status have been reported to exhibit a low level of correlation [84,85,87]. It might simply suggest that elderly patients without any comorbidity were predominantly selected for enrollment in the trials.

We found several trials that included not only elderly patients but also non-elderly patients with a poor performance status [10–29], where the treatment efficacy for both groups was evaluated as a single group. Of these trials, Frasci et al. performed a subset analysis comparing elderly patients with non-elderly patients with a poor performance status in a phase II study of carboplatin and etoposide and concluded that the tumor responses and overall survival times for the two populations were clearly different [27]. Edelman et al. has also documented different toxicity and efficacy profiles for these two groups [28]. Thus, elderly patients and non-elderly patients with a poor performance status seem to compose distinct populations and should be accrued separately in clinical trials, even if the primary endpoint for each population is identical.

Quality-of-life is an extremely important issue in elderly patients with advanced NSCLC; however, formal quality-of-life assessments were only performed in a few elderly-specific clinical trials. Of these, the ELVIS trial demonstrated that single-agent chemotherapy with vinorelbine clearly improved quality-of-life [33]. Another phase III trial revealed that the baseline assessment of quality-of-life was a prognostic factor [88]. Quality-of-life assessments are particularly important when the difference in survival between two treatment strategies is very small and quality-of-life becomes one of the major determinants of treatment choice. Thus, the results obtained from the two phase III trials indicate that

an assessment of quality-of-life is necessary for identifying elderly patients with advanced NSCLC who are candidates for systemic chemotherapy.

5. Conclusion

Our review revealed that (i) the definition of "elderly" varied from trial to trial, and "elderly" patients were usually defined using their calendar age in most of the elderly-specific trials; (ii) the quality of the elderly-specific clinical trials was generally poor because most trials included only a small number of patients, often did not include a statement of written informed consent, were reported in abstract-form only and the enrolled patients were unlikely to have comorbidities suggesting the presence of a study bias; and (iii) single-agent chemotherapy with new drugs is promising for the treatment of elderly patients with advanced NSCLC. Well-designed prospective trials with a sufficient patient sample size are needed to elucidate many unanswered questions regarding the optimal and most effective treatments for elderly patients.

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Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer

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Summary

Background: Gefitinib ('Iressa', ZD1839), an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (EGFR-TKI), has shown antitumor activity in refractory patients with non-small-cell lung cancer (NSCLC) in clinical trials. We have retrospectively analyzed the efficacy and tolerability of gefitinib in patients with advanced NSCLC treated at Okayama University Hospital.
Methods: We reviewed the clinical records of 57 patients with advanced NSCLC who had received 250 mg/day gefitinib at our hospital between November 2000 and May 2003. Correlations between the sensitivity of brain metastases and extracranial disease following treatment with gefitinib were also investigated.
Results: Extracranial objective responses were observed in 15 (27%; 95% confidence interval 15.8–40.3%) patients. Fourteen out of 57 patients had brain metastases; six experienced objective responses (one complete response, CR and five partial responses, PR) and eight had stable disease (SD) in the brain. Seven out of 14 patients with brain metastases experienced objective responses in their extracranial tumors and, interestingly, objective responses in the brain were observed in six (86%) of these patients. Multivariate analysis found that advanced age (≥70 years) and the presence of brain metastases were associated with clinical response to gefitinib ($P = 0.01$ and 0.05, respectively), and that female patients were more likely to respond. Median survival and median duration of response were 9.1 and 7.7 months, respectively. The majority of adverse events (AEs) were mild and reversible skin and gastrointestinal disorders, with grade 3 adverse events observed in six (11%) patients.

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Conclusions: This retrospective analysis has found that gefitinib is effective and well tolerated in patients with refractory NSCLC, confirming previous phase II trial data. Interestingly, gefitinib appeared to be effective for brain metastases as well as extracranial tumors. Further prospective trials are warranted to evaluate the efficacy of gefitinib in elderly patients and in patients with brain metastases.

1. Introduction

Lung cancer is the leading cause of cancer deaths in many countries. Non-small-cell lung cancer (NSCLC) accounts for approximately 75% of lung cancer cases, with the majority of patients having inoperable locally advanced or metastatic disease at the time of diagnosis, reflected by the low 5-year survival rate for all stages (currently 13%) [1]. Although cisplatin-based chemotherapy has been used extensively for the past two decades to treat patients with advanced NSCLC, the survival benefit remains modest [2]. A recent analysis of large phase III trials has shown that the impact of new chemotherapy combinations on survival is minimal compared with older regimens, with overall response rates of approximately 30%, median survival benefits of 8–9 months, and 1-year survival rates of approximately 30% [3]. New therapies are required that are effective against locally advanced or metastatic NSCLC.

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because it is expressed in a variety of tumors, including NSCLC [4], and elevated EGFR expression levels have been associated with a poor prognosis in lung cancer patients [5]. Several EGFR-targeted agents have been developed, including gefitinib ('Iressa', ZD1839), an orally active anilinoquinazoline compound that inhibits EGFR tyrosine kinase activity [6]. In two large, well-designed, phase II clinical trials, refractory patients with NSCLC experienced overall response rates of 11.8–18.4%, median survival benefits of 6.5–7.6 months, and 1-year survival rates of 29–35% [7,8].

At present, it remains unclear whether gefitinib is effective against brain metastases and whether the sensitivity of brain metastases to gefitinib correlates with the sensitivity of extracranial disease. Therefore, we have retrospectively reviewed the efficacy of gefitinib in patients with advanced NSCLC treated at our hospital, and have focused specifically on the response of brain metastases to gefitinib.

2. Patients and methods

2.1. Patients

Between November 2000 and May 2003, 57 patients were treated with 250 mg/day gefitinib in Okayama University Hospital. All patients had been diagnosed with advanced NSCLC; the staging procedure included medical history, physical examination, laboratory tests, chest radiograph, fiberoptic bronchoscopy, computed tomographic scans of the chest and abdomen, magnetic resonance imaging of the brain, and a radionuclide bone scan (if medically indicated). Written, informed consent was obtained from each patient before gefitinib treatment began.

2.2. Assessment of antitumor activity and toxicity

Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) in accordance with the standard Response Evaluation Criteria in Solid Tumors [9]. Extracranial disease was defined as the primary tumor plus extracranial metastases; tumor responses of extracranial disease and brain metastases were also assessed separately. Tumor responses were assessed every 4 weeks. Adverse events (AEs) were graded according to a modified version of the National Cancer Institute Common Toxicity Criteria [10]. Subjective symptoms were assessed based on routine interview every 2 weeks.

2.3. Statistical analysis

Statistical analyses were performed using the StatView® 5.0 program (BrainPower Inc., Calabasas, CA, USA). The association between the response to gefitinib of extracranial disease and brain metastases was evaluated using Fisher's exact test. Multivariate analysis was performed with a logistic regression model for potential factors linked to gefitinib sensitivity; these included performance

status, age, gender, histology, smoking history, and disease stage. Survival curves were calculated using the Kaplan–Meier method and *P*-values of <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Table 1 summarizes the characteristics of the 57 patients analyzed. The median age was 58 (range 29–82) years and the majority of patients had non-squamous histology (89%), a history of smoking (70%), and metastatic disease (79%); one patient with multiple primary NSCLC (stage IA) was also included. Median follow-up time was 11.8 months. Six patients (11%) had not received any prior chemotherapy: one with poor pulmonary function due to severe chronic obstructive pulmonary disease, one with chronic heart failure, one with poor performance status, one who had been enrolled in a clinical trial, and two who had refused other treatment options. All patients had extracranial disease, except for one patient who received gefitinib as postoperative adjuvant therapy without any evaluable lesions. Out of the 57 patients, 14 (25%) had brain metastases.

Table 1 Patient characteristics

Number of patients	57
Age, median (range)	58 (29–82)
Gender, male/female	38/19
Performance status	
0	9
1	32
2	10
3	4
4	2
Stage	
IA	1
IIIA	3
IIIB	7
IV	45
Postoperative recurrence	1
Histology	
Adenocarcinoma	45
Squamous cell carcinoma	6
Large-cell carcinoma	2
Large-cell neuroendocrine carcinoma	2
Adenosquamous-cell carcinoma	1
Bronchioalveolar carcinoma	1
Smoking	
Never	17
Former	13
Current	27
Number of prior chemotherapy regimens	
0	6
1	19
2	16
≥3	16
Prior cisplatin-based chemotherapy	
Yes	45
No	12
Prior thoracic irradiation	
Yes	35
No	22
Brain metastases	
Yes	14
No	43

3.2. Treatment administration

All patients received 250 mg/day gefitinib, which continued uninterrupted until PD, unacceptable toxicity, or withdrawal from treatment. Median duration of treatment was 3.1 (range 0.2–23.9) months and was, as expected, longer for responders than for nonresponders (8.4 versus 1.9 months, respectively).

3.3. Response and overall survival

Fifty-six patients (98%) were evaluable for efficacy of gefitinib in extracranial disease and/or brain metastases. Fifteen patients achieved PR (27%; 95% confidence interval 15.8–40.3%) and SD was observed in 27 patients (46%). The median duration of objective tumor response was 7.7 months with a range from 4.1 to 24.0 months. Forty-six out of 57 patients (81%) were symptomatic at the start of treatment, mainly with specific pulmonary problems. Nearly one-third (32.6%) of symptomatic patients experienced symptom improvement (median time to symptom improvement was 18 days), and those who experienced tumor response were more likely to experience improvements in disease-related symptoms (nine out of 15 patients who experienced tumor response versus six out of 14 patients who did not experience tumor response; $P = 0.002$). The median survival has not been reached, while the median follow-up time was 11.8 months.

3.4. Effect of gefitinib on brain metastases

Fourteen out of 57 patients (25%) had brain metastases (Table 2); of these, 12 had adenocarcinoma and six had received prior cranial irradiation. The median maximum size of brain metastases

Table 2 Clinical characteristics of 14 patients with brain metastasis

Case number	Age	Gender	Smoking	Histology	PS	Prior chemo	Extracranial disease	Prior brain RT	Interval between RT and gefitinib treatment (months)	Objective response	
										Extracranial disease	Brain
1	40	M	Never	Ad	1	Yes	Lung, liver	Yes	4.9	PR	CR
2	29	F	Never	Ad	1	Yes	Lung	No	—	PR	PR
3	60	F	Never	Ad	2	Yes	LN	Yes	1.9	PR	PR
4	73	M	Former	Ad	2	Yes	Lung, bone	No	—	PR	PR
5	54	F	Never	Ad	4	Yes	Lung, LN, liver	Yes	7.1	PR	PR
6	59	F	Never	Ad	1	Yes	Lung, bone	Yes	2.0	PR	PR
7	71	M	Current	Ad	1	Yes	Lung, LN, pleura	No	—	PR	SD
8	69	M	Former	Ad	1	Yes	Lung, LN, pleura	No	—	SD	SD
9	59	F	Never	Ad	1	Yes	Bone	No	—	SD	SD
10	42	F	Never	Ad	1	Yes	Lung, LN, bone	No	—	SD	SD
11	33	M	Current	La	1	Yes	Lung, adrenal	No	—	PD	SD
12	68	M	Former	LC	3	Yes	Lung, LN	Yes	0.4	PD	SD
13	44	F	Former	Ad	1	Yes	Lung, LN, liver	Yes	1.1	PD	SD
14	55	M	Current	Ad	1	Yes	Lung, LN, bone	No	—	PD	SD

PS, performance status; RT, radiation; M, male; F, female; Ad, adenocarcinoma; La, large-cell carcinoma; LC, large-cell neuroendocrine carcinoma; LN, lymph node; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

Table 3 Multivariate analysis of the hazard ratios for various factors on objective response to gefitinib

Factors	Tumor response, *n* (%)	Odds ratio (95% CI)	*P*-value
Tumor histology			
Non-adenocarcinoma	2 (18)	0.51 (0.06–4.35)	0.54
Adenocarcinoma	13 (29)	1	
Disease stage			
I–IV	10 (26)	0.23 (0.04–1.56)	0.13
Postoperative recurrence	5 (28)	1	
Performance status			
2–4	5 (31)	2.94 (0.47–18.3)	0.25
0–1	10 (25)	1	
Smoking status			
BI ≥ 600	7 (25)	7.27 (0.60–88.3)	0.12
BI < 600	8 (29)	1	
Gender			
Female	6 (32)	10.6 (0.89–125.3)	0.06
Male	9 (24)	1	
Brain metastasis			
Yes	7 (50)	7.28 (0.98–54.2)	0.05
No	8 (19)	1	
Age (years)			
≥70	5 (36)	26.9 (2.19–331.1)	0.01
<69	10 (24)	1	

CI, confidence interval; BI, Brinkman index.

was 3.0 cm, with a median of four metastases per patient. The median interval between cranial irradiation and gefitinib treatment was 2.0 months (range; 0.4–7.1 months) and the median delivered dose was 30 Gy. Control of brain metastases was achieved in all 14 patients; one (7.1%) had a CR, five (35.7%) had PR, and eight (57.1%) had SD. Seven out of 14 patients with brain metastases experienced objective responses in their extracranial tumors, six of whom also experienced objective responses in the brain (four out of six patients (67%) had received prior cranial radiotherapy, but three out of four patients (75%) had shown definite disease progression in the brain before gefitinib treatment was started). The median duration of tumor response in the brain was 8.8 months.

3.5. Analysis of factors affecting gefitinib sensitivity

The association between several clinicopathologic factors and response to gefitinib was evaluated with a logistic regression model. Multivariate analysis found that patients aged ≥70 years and those with brain metastases were more sensitive to gefitinib ($P = 0.01$ and 0.05, respectively); in addition, female patients tended to respond well to gefitinib ($P = 0.06$) (Table 3); however, in our series, there were no other possible factors affecting the sensitivity to gefitinib.

3.6. Toxicity

All 57 patients were evaluable for safety. The most common AE was mild to moderate, reversible, grade 1/2 skin rash (67%); grade 1/2 diarrhea (44%), hepatotoxicity (elevated ALT/AST, 25%), and nausea and vomiting (16%) were also observed. Grade 3 toxicity was observed in six patients (11%); three had skin rash, two had hepatotoxicity and one had diarrhea. No grade 4 AEs were observed. No patients experienced interstitial lung disease; the condition was suspected in two patients, but autopsy revealed disease progression due to lymphangitis carcinomatosa. Sixteen out of 57 patients required a treatment interruption (median duration 15 days), which was due to AEs in 14 patients (88%) and withdrawal from treatment in two patients (12%). The main AEs included hepatotoxicity (four patients), infection (four patients), skin reaction (three patients), nausea/vomiting (two patients), and diarrhea (one patient). By June 2003, gefitinib treatment had been discontinued in 39 out of 57 patients; disease had progressed

in 33 patients (85%) and six patients (15%) had had treatment withdrawn due to gefitinib-related AEs (grade 3 infection [four patients], grade 2 nausea/vomiting and grade 2 hepatotoxicity [one patient each]). No treatment-related death was encountered.

4. Discussion

We previously published the first case report to suggest that gefitinib might be effective in patients with brain metastases [11], and Cappuzzo et al recently described a small case series of patients whose brain metastases, as well as extracranial disease, responded to gefitinib (although no details were given of whether there was any correlation between the efficacy of gefitinib for brain metastases and extracranial disease) [12]. In this retrospective analysis of 57 patients with advanced NSCLC, we have shown that gefitinib is effective against brain metastases, with a response rate equivalent to that obtained against extracranial disease. Furthermore, patients with brain metastases whose extracranial disease did not respond to gefitinib were highly unlikely to experience objective responses in the brain.

To our knowledge, this is the first time that the sensitivity of brain metastases to gefitinib has been strongly correlated to that of extracranial disease. Preclinical studies have shown that gefitinib has therapeutic activity against brain tumors in mice [13], although data on non-tumor-bearing rats showed that distribution of [^{14}C] gefitinib in the central nervous system of rats was low [14]. Of the 14 patients in our retrospective analysis with brain metastases, six patients had received cranial irradiation before gefitinib therapy was started and four of these patients responded to gefitinib (in one patient gefitinib was sequentially administered after radiotherapy). However, three patients with progressive disease of brain metastases and two patients with asymptomatic brain metastases who had not received cranial irradiation responded to gefitinib. Therefore, it remains unclear whether sensitivity to gefitinib might be influenced by cranial irradiation. Further prospective clinical trials may be warranted to clarify the role of gefitinib in patients with brain metastasis.

Factors that definitely predict response to gefitinib have yet to be identified, unlike HER-2/neu for trastuzumab and c-kit or BCR-ABL for imatinib [15,16]. Factors that may predict response to gefitinib include female gender and adenocarcinoma [7], along with bronchioalveolar histology and smoking history [17]. In contrast, our analysis revealed that neither tumor histology nor smoking history influenced response to gefitinib, a discrepancy that might result from differences in (i) patient population (an especially small population in our study), (ii) ethnicity, (iii) response criteria, or (iv) treatment schedule. We found that patient age significantly affected sensitivity to gefitinib, an observation that supported the findings of Gridelli et al., who found gefitinib to be active in elderly patients [18]. Interestingly, we also demonstrated that the presence of brain metastases was one of the predictive factors for gefitinib sensitivity, although the reasons why these two factors influenced sensitivity to gefitinib in our analysis remain to be determined.

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ORIGINAL ARTICLE

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Clinical and pharmacokinetic study of docetaxel in elderly non-small-cell lung cancer patients

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Abstract *Purpose*: To evaluate the usefulness and pharmacokinetics of docetaxel in the treatment of elderly patients with advanced non-small-cell lung cancer. *Patients and methods*: Chemotherapy-naive elderly patients (aged at least 76 years) with locally advanced or metastatic non-small-cell lung cancer were accrued. Eligible patients received at least two cycles of docetaxel at a dose of 60 mg/m^2 on day 1 over 1 h every 3 weeks. Patients who were considered ineligible for this study were also registered. Symptom control was assessed using a questionnaire during the treatment period. The pharmacokinetics of docetaxel were evaluated in the first cycle of chemotherapy. *Results*: Of 35 elderly patients, 15 (43%) met the study eligibility criteria. The reasons for ineligibility consisted mainly of poor performance status, poor bone marrow function, and hypoxemia (six patients each). A total of 49 cycles of chemotherapy (median 2 cycles, range 1–12 cycles) were administered to the eligible patients, six of whom achieved a partial response (overall response rate 40%, 95% confidence interval 15–65%). The major toxicity was hematologic, with grade 3 or greater neutropenia and grade 3 neutropenic fever developing in 13 patients (87%) and five patients (33%), respectively. Symptoms, as assessed in terms of the symptom control score, did not clearly decline during the treatment period. The values (mean ± SD) of C_{max}, $AUC_{0 \rightarrow inf}$, and $t_{1/2}$ were 1.35 ± 0.32 μg/ml, 1.79 ± 0.52 μg h/ml, and 4.1 ± 2.3 h, respectively. *Conclusions*: Although the validity of the results of this study is limited due to the small sample size, docetaxel appears effective in selected elderly patients with advanced non-small-cell lung cancer.

Keywords Docetaxel · Elderly · Non-small-cell lung cancer · Pharmacokinetics · Symptom control assessment

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Introduction

The incidence and mortality rate of lung cancer are increasing in Western countries and Japan. In the United States, the incidences of lung cancer per 100,000 persons from 1994 through 1997 were 565.5 for men and 294.1 for women, and peaked between the ages of 75 and 79 years [18]. In Osaka prefecture, Japan, the incidence also peaked above 74 years of age in the same period [18]. In addition, the mortality rates of lung cancer patients older than 74 years were 42.2% for men and 53.4% for women in Japan in 1999 [14]. Accordingly, treatment of elderly patients with lung cancer is of particular concern.

Cisplatin-based chemotherapy has been proven to improve survival of patients with advanced non-small-cell lung cancer (NSCLC) compared to best supportive care [11]. However, this benefit is modest and is limited to patients who have favorable conditions such as good performance status (PS) and younger age. In clinical trial, the upper age limit is usually set at 65 or 70 years, or 75 years at most; therefore, patients older than 75 years have been excluded from clinical trials.

The diversity of the elderly population makes it particularly difficult to determine the appropriateness of chemotherapy. The prevalence of comorbidity, functional limitations, socioeconomic restrictions, and geriatric syndromes appears to increase in patients greater than 74 years of age. Although no precise formulae are available for determining the physiologic age of patients, Balducci and Extermann have noted that an age of 75 years might represent a reasonable cut-off point to define older individuals [1]. In addition, it remains unclear how many patients can be treated with chemotherapy among all elderly patients with NSCLC, since there have been few reports on the proportion of patients eligible for chemotherapy among all elderly individuals with advanced NSCLC.

New anticancer agents such as vinorelbine, gemcitabine, and taxanes were developed and introduced for the treatment of NSCLC in the 1990s [2]. Among these agents, docetaxel is the first agent to be approved in Japan. The approved dose (60 mg/m^2) in Japan is lower than that (100 mg/m^2) in the United States and European countries [4]. However, this low dose of docetaxel is sufficiently effective with a low incidence of toxicities such as hypersensitivity and peripheral edema [4, 9].

On the basis of these considerations, a phase II study of docetaxel in elderly patients with advanced NSCLC was conducted in order to (1) evaluate the proportion of patients eligible for this study among all elderly patients with advanced NSCLC, (2) assess the efficacy and safety of docetaxel in the treatment of selected elderly patients, (3) examine the tolerability of this treatment from the view point of symptom control assessment during the treatment period, and (4) examine the pharmacokinetic profile of docetaxel in the elderly.

Patients and methods

Eligibility criteria

Chemotherapy-naive elderly patients (aged at least 76 years) with histologically or cytologically confirmed locally advanced (stage IIIA with N2 or IIIB) or metastatic (stage IV) NSCLC were accrued to this study. Eligibility criteria included an Eastern Cooperative Oncology Group PS of two or less, at least one measurable or assessable lesion, and life expectancy of 3 months or longer. Before enrollment, a complete medical history was obtained from each patient, and each underwent physical, laboratory, and staging work-up examinations. Laboratory examinations included complete blood cell counts with differential, routine serum chemistry and tumor marker analyses, 24-h creatinine clearance evaluation, arterial blood gas analysis, urinalysis, electrocardiogram, and pulmonary function tests. Staging work-up examination consisted of chest radiograph, computerized tomography (CT) of the chest and abdomen, magnetic resonance imaging of the brain, radionucleotide bone scan, and fiberoptic bronchoscopy. On laboratory examination, patients were required to have adequate organ function, as evidenced by a leukocyte count between 4000 and 12,000/μl, a neutrophil count of 2000/μl, a hemoglobin level of 9.5 g/dl, a platelet count of 100,000/μl, a total bilirubin level of 1.5 mg/dl, AST and ALT levels 2.5 times the upper limit of the normal range, a serum creatinine level not more than the upper limit of the normal range, and a PaO_2 of 65 mmHg. Patients with active infection, interstitial pneumonia, peripheral edema, or pleural or pericardial effusion that required drainage (patients with pleural effusion who had been successfully treated with agents other than anticancer drugs were eligible), a history of severe hypersensitivity, symptomatic brain metastasis, or active concomitant malignancy were excluded. Patients who were for other reasons considered not suited for study entry by the treating physician were also excluded. In addition, concomitant use of ketoconazole, miconazole, erythromycin, or clarithromycin was not permitted in this study, because it is possible that docetaxel metabolism is inhibited by these agents via liver cytochrome P450 isozyme CYP3A [7].

Written informed consent was obtained from all patients. Three institutions participated in this study, and each of their Institutional Review Boards approved this study. The registration office (National Shikoku Cancer Center) entered the patients after verification of eligibility. Patients who were considered ineligible for this study were also registered in order to assess the reasons for ineligibility and estimate the proportion of eligible patients among the entire elderly population with advanced NSCLC.

Chemotherapy

Eligible patients received at least two cycles of docetaxel monotherapy. Docetaxel was given at a dose of 60 mg/m^2 on day 1 and repeated every 3 weeks. It was diluted in 500 ml 5% glucose or 0.9% saline solution, and was infused over a 1-h period. Antiemetic treatment was left to the treating physician. Prophylactic administration of dexamethasone was used to prevent fluid retention or hypersensitivity reaction, as well as for the prevention of emesis. Administration of granulocyte-colony stimulating factor (G-CSF) was allowed when grade 4 neutropenia or grade 3 neutropenic fever occurred. This administration was continued until the neutrophil count recovered to 5000/μl. The dose of docetaxel was reduced to 50 mg/m^2 in the presence of grade 4 hematologic toxicities lasting 3 days or when grade 3 non-hematologic toxicities had developed in the prior cycle of chemotherapy. Chemotherapy was withdrawn when similar toxicities were observed at this reduced dose level. In addition, docetaxel administration was postponed for up to 2 weeks (a maximum 6 weeks between administrations) when leukocyte, neutrophil, and platelet counts were less than 4000,

2000, and 100,000/μl, respectively. Chemotherapy was discontinued when delay of hematologic recovery continued for over 2 weeks. Other criteria for early interruption of this protocol treatment included progression of disease, emergence of intolerable toxicities, and withdrawal of consent. In addition, chemotherapy was discontinued for patients who were assessed as having stable disease after completion of two cycles of chemotherapy. Responders were allowed to continue this treatment until disease progression or the emergence of intolerable toxicities.

Toxicity and response evaluation

For evaluation of response and toxicity, all patients underwent as inpatients a series of examinations consisting of complete blood cell counts with differential, routine chemistry profiles, and chest radiograph on at least a weekly basis during the treatment period and then on a monthly basis. In addition, the patients' clinical characteristics such as symptoms, body temperature, and weight were periodically recorded. Evaluation of target lesions was performed after each cycle of chemotherapy, and the same examinations as for the staging work-up study were performed after completion of treatment.

Responses were assessed using the World Health Organization criteria [8]. The response to treatment, including eligibility and assessability, was determined for each patient by extramural reviewers. Complete response was defined as the disappearance of all measurable lesions for at least 4 weeks. Partial response (PR) was defined as a 50% decrease in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks without the development of new lesions. Progressive disease (PD) was defined as a 25% increase in the sum of the products of the perpendicular diameters of all measurable disease or the appearance of new lesions. If no response or progression of disease occurred during therapy, treatment outcome was considered to be no change (NC). Toxicities were assessed and graded using the National Cancer Institute Common Toxicity Criteria, version 2.0 (the Japan Clinical Oncology Group version) [10]. The worst degree of toxicity experienced throughout the treatment was computed for each patient.

Symptom control assessment

A quality-of-life (QOL) questionnaire for cancer patients treated with anticancer drugs (QOL-ACD) has been developed in Japan [5]. It is a 22-item questionnaire that covers four domains consisting of functional, physical, mental, and psychosocial well-being. In addition, global QOL is assessed using a face scale. In this study, assessment of symptoms during chemotherapy was performed using a questionnaire that consisted of four items selected from the QOL-ACD questionnaire (feeling, appetite, vomiting, and sleep) and an additional item concerning respiratory condition (cough and sputum). Assessment of global QOL using the face scale was also performed. Each patient was asked to fill in this questionnaire at the time of study entry (baseline symptom score) and immediately before each cycle of chemotherapy. Severity of each symptom during chemotherapy was scored using a visual analogue scale and was assessed compared with the baseline value.

Pharmacokinetic evaluation

The pharmacokinetics of docetaxel were studied in the first cycle of chemotherapy. Samples were taken at the following time points: predose, midinfusion, end of infusion, and 30 min and 2, 3, 5, 7, 23, 47 and 71 h after infusion. All blood samples were immediately centrifuged and the heparinized plasma was stored at −20°C until analysis. Subsequent assays and pharmacokinetic analysis were performed based on a previously described method [13]. Briefly, docetaxel concentrations in plasma were determined by high-performance liquid chromatography with UV detection. Docetaxel and internal standard were determined by a UV detector adjusted to 225 nm, and peak heights were used for quantification. Pharmacokinetic parameters were calculated using WinNonlin computer software (Pharsight, Mountain View, Calif.). The maximum plasma concentration (C_{max}) was obtained from the actual value. The terminal rate constant (k) was determined by log-linear regression analysis of the terminal phase of the plasma concentration vs time curve. The terminal half-life time ($t_{1/2}$) was calculated by the equation $t_{1/2} = 0.693/k$. The area under the concentration vs time curve (AUC) was calculated by the linear trapezoidal rule up to the last measurable data points with extrapolation to infinity. The clearance (CL) was calculated by dividing the dose received by the AUC.

Statistical considerations

The sample size of this study was determined with the assumption of an expected response rate of 20%, with a 95% confidence interval (CI) of ±10%. Accrual of 61 patients was therefore required for this study. Statistical analyses were performed using the SPSS Base System and Advanced Statistics programs (SPSS, Chicago, Ill.). The significances of differences between baseline and during-treatment or post-treatment symptom scores were determined using Student's paired *t*-test. The global QOL score was similarly analyzed. Survival time was defined as the period from initiation of treatment to death or last follow-up evaluation. In addition, time to progression was defined as the period from initiation of treatment to PD. Patients who received additional thoracic radiotherapy were censored at the start of

irradiation. Survival curves were calculated using the method of Kaplan and Meier.

Results

Patient characteristics

Between November 1999 and December 2001, 35 elderly patients with advanced NSCLC were accrued to this study. Of these, 15 (43%) met the study eligibility criteria. Although the sample size of this study was designed to be 61 patients on an eligible patient basis, the study was terminated early due mainly to the slow rate of accrual of patients.

The characteristics of the entire group of patients and eligible patients are listed in Table 1. The median ages and age ranges were similar for the two groups. However, the proportions of patients with a poor PS, adenocarcinoma, or metastatic disease were higher in the entire group than in the eligible group. The proportion of patients with weight loss was not determined in the entire group, since assessment of weight loss was not required for registration of patients ineligible for this study. The reasons for ineligibility for study entry were poor PS ($n=6$), poor bone marrow function ($n=6$), hypoxemia ($n=6$), life expectancy less than 3 months ($n=4$), physician's discretion ($n=4$), symptomatic brain metastasis ($n=2$), double cancer ($n=2$), poor renal function ($n=1$), infection ($n=1$), and interstitial lung disease ($n=1$). More than one reason was noted in seven patients. In addition, two patients refused chemotherapy. Among ineligible patients, two received chemotherapy; one with anemia received docetaxel at a dose of 60 mg/m^2, and the other with anemia and hypoxemia received vinorelbine monotherapy. The serum albumin values (means ± SD) were 3.6 ± 0.30 g/dl in 15 eligible patients and 3.9 ± 0.39 g/dl in 20 ineligible patients. In addition, the value of plasma alpha-1 acid glycoprotein (AAG), which was measured in ten eligible patients, was 1.22 ± 0.39 g/l.

Table 1 Patient characteristics (*NE* not evaluated)

	All patients ($n=35$)	Eligible patients ($n=15$)
Age (years)		
Median	78	78
Range	76–87	76–87
Sex		
Male	27	12
Female	8	3
ECOG performance status		
0	4	3
1	19	10
2	6	2
3	3	0
4	3	0
Histology		
Adenocarcinoma	18	7
Squamous cell	14	6
Adenosquamous cell	2	1
Not otherwise specified	1	1
Stage		
IIIA	8	3
IIIB	8	6
IV	19	6
Weight loss		
<5%	NE	12
≥5%	NE	3

Chemotherapy outcome

A total of 49 cycles of chemotherapy were administered to 15 eligible patients. The median number of chemotherapy cycles was two (1 cycle in two patients, 2 cycles in six, 3 cycles in four, 5 cycles in one, 6 cycles in one, and 12 cycles in one). Two patients who had disease progression or developed docetaxel-related interstitial lung toxicity received only one cycle of chemotherapy. Four patients underwent reduction of dose of docetaxel because of grade 4 neutropenia lasting for 3 days ($n=3$), grade 3 neutropenic fever ($n=1$), or grade 3 nausea ($n=1$). One patient developed both grade 4 neutropenia and grade 3 nausea. In addition, the median interval between each cycle of chemotherapy was 22 days (range 19–30 days).

Of the 15 patients, 6 achieved PR, 6 NC, and 2 PD. Response was not evaluated for one patient who developed docetaxel-related interstitial pneumonia. The overall response rate was 40%, with a 95% CI of 15–65%. Four patients with stage IIIA ($n=3$) or IIIB disease ($n=1$) received additional thoracic radiotherapy. The plasma AAG levels of two patients with PD were 1.85 and 1.79 g/l, respectively, which were the highest and the second highest values in this study. With a median follow-up period of 27.9 months (range 16.2–42.5 months), median progression-free survival time was 6.1 months (95% CI 5.6–6.6 months). At the time of analysis, 11 patients had died and four were still alive. The cause of death was directly related to NSCLC in ten patients and unrelated in one (interstitial pneumonia). This complication of interstitial pneumonia, occurring in another patient who developed docetaxel-related lung toxicity, was observed more than 12 months after completion of chemotherapy. The median survival time was 15.6 months (95% CI 11.4–19.8 months), with 1-year and 2-year survival rates of 73.3% and 37.3%, respectively.

The toxicities observed in the 15 patients during treatment and the follow-up period are listed in Table 2. The major toxicity was myelosuppression, with grade 3 or higher leukopenia and neutropenia observed in 9 patients (60%) and 13 patients (87%), respectively. Grade 3 neutropenic fever occurred in five patients (33%). G-CSF was administered to 13 patients (87%) over a median duration of 4 days (range 2–6 days). Grade 3 nonhematologic toxicities observed in this study included fatigue (33%), dyspnea (13%), electrolyte dis-