of the results presented here, we are currently preparing a Phase II study.

In conclusion, the MTD was not reached in the present study, although the dose of radiation was escalated to 72 Gy in 48 fractions. Acute toxicities were relatively mild. However, a dose of 66 Gy in 44 fractions was adopted for the present study because late toxicity data were insufficient.

References

1. Furuse K, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small cell lung cancer. *J Clin Oncol* 1996;17:2692–2699.
2. Fournel P, Robinet G, Thomas P, *et al.* Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemo-radiotherapy in locally advanced non-small-cell lung cancer: Group Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerogie NPC 95-01 Study. *J Clin Oncol* 2005;23: 5910–5917.
3. Zatloukal P, Petruzelka L, Zemanova M, *et al.* Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: A randomized study. *Lung Cancer* 2004;46:87–98.
4. Curran W, Scott C, Langer C, *et al.* Long term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresectable stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003;22:621 (abstr 2499).
5. Schaake-Koning C, Vand den Bogaert W, Dalesio O, *et al.* Effect of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524–530.
6. Tada T, Minakuchi K, Matsui K, *et al.* A single institutional subset analysis of the WJLCG study comparing concurrent and sequential chemoradiotherapy for stage III non-small-cell lung cancer. *Radiat Med* 2004;22:163–167.
7. Le Chevalier T, Arriagada R, Tarayre M, *et al.* Significant effect of adjuvant chemotherapy on survival in locally advanced non-small-cell lung carcinoma [Letter]. *J Natl Cancer Inst* 1992;84:58.
8. Socinski MA, Rosenmann JG, Halle JS, *et al.* Induction carboplatin/paclitaxel followed by concurrent carboplatin/paclitaxel and dose-escalating conformal thoracic radiation therapy in unresectable stage IIIA/B non-small cell lung cancer: A modified phase I trial. *Cancer* 2000;89:534–542.
9. Rosenmann JG, Halle JS, Socinski MA, *et al.* High dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: Technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys* 2002;54:348–356.
10. Blackstock AW, Lesser GJ, Fletcher-Steede J, *et al.* Phase I study of twice-weekly gemcitabin and concurrent thoracic radiation for patients with locally advanced non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2001;51:1281–1289.
11. Blackstock AW, Ho C, Butler J, *et al.* Phase Ia/Ib chemo-radiation trial of gemcitabin and dose-escalated thoracic radiation in patients with stage III A/B non-small cell lung cancer. *J Thorac Oncol* 2006; 1:434–440.
12. Withers HR, Taylor JMG, Maciewjewski B, *et al.* The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol* 1988;27:131–146.
13. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205–216.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete evaluations. *J Am Stat Assoc* 1958;53:457–481.
15. Kong FM, Haken RKT, Schipper MJ, *et al.* High dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005;63:324–333.
16. Emami B, Lyman J, Brown A, *et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21: 109–122.
17. Atsumi K, Shioyama Y, Nakamura K, *et al.* Predictive factors of esophageal stenosis associated with tumor regression in radiation therapy for locally advanced esophageal cancer. *J Radiat Res* 2010;51: 9–14.
18. Saito H, Takada Y, Ichinose Y, *et al.* Phase II study of etoposide and cisplatin with concurrent twice-daily thoracic radiotherapy followed by irinotecan and cisplatin in patients with limited-disease small-cell lung cancer: West Japan Thoracic Oncology Group 9902. *J Clin Oncol* 2006;24:5247–5252.
19. Takada M, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: Results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20:3054–3060.
20. Tsujino K, Hirota S, Kotani Y, *et al.* Radiation pneumonitis following concurrent accelerated hyperfractionated radiotherapy and chemotherapy for limited-stage small-cell lung cancer: Dose-volume histogram analysis and comparing with conventional chemoradiation. *Int J Radiat Oncol Biol Phys* 2006;64:1100–1105.
21. Schild SE, McGinnis WL, Graham D, *et al.* Results of a phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1106–1111.
22. Nishimura Y, Nakagawa K, Takeda K, *et al.* Phase I/II trial of sequential chemoradiotherapy using novel hypoxic cell radiosensitizer, doranidazole (PR-350), in patients with locally advanced non-small-cell lung cancer (WJTOG-0002). *Int J Radiat Oncol Biol Phys* 2007;69: 786–792.
23. Marks LB, Garst J, Socinsky MA, *et al.* Carboplatin/paclitaxel or carboplatin/vinorelbine followed by accelerated hyperfractionated conformal radiation therapy: Report of a prospective phase I dose escalation trial from the Carolina conformal therapy consortium. *Clin Oncol* 2004;22:4329–4340.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Diagnostic Factors of Standard Bronchoscopy for Small (≤15 mm) Peripheral Pulmonary Lesions: A Multivariate Analysis

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Abstract

Background The aim of this study was to evaluate the factors contributing to an accurate diagnosis of small (≤15 mm) peripheral pulmonary lesions (PPLs) by standard bronchoscopy and to determine the most suitable technology for such a diagnosis.

Objective Bronchoscopy was performed for 115 PPLs (≤15 mm diameter) on chest computed tomography (CT) between August 2003 and December 2006.

Methods Univariate and multivariate analyses were conducted retrospectively with the R software.

Results The diagnostic yield of the 115 PPLs was 65.2%; the yield was 61.9% and 69.2% for the malignant and benign lesions, respectively. In the univariate analysis, the approach to the lesion contributed the most to successful diagnosis, followed by skill and the use of hemostasis. In the multivariate analysis, the most important factor was approach, followed by lower lobe lesion and the use of hemostasis. Although it was better to use a sedative, operator skill was not a contributing factor.

Conclusion The approach to the lesion is the most important factor for a successful diagnosis of PPLs by bronchoscopy. Bronchoscopy is time consuming and painful; therefore, it is very important to establish an accurate diagnosis as soon as possible. Further, endobronchial ultrasonography with a guide sheath (EBUS-GS) and navigation systems are useful tools for the diagnosis of small PPLs.

Key words: small peripheral pulmonary lesions, PPLs, bronchoscopy, diagnostic factor

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Introduction

Lung cancer, one of the most frequently occurring malignant neoplasms, is the leading cause of cancer-related death among both men and women in developed countries (1). Following the recent advances in computed tomography (CT) equipment and their widespread use, particularly with the introduction of low-dose helical CT to examine lung cancer, the detection rate of peripheral pulmonary lesions (PPLs) is increasing (2). Especially, with the increasingly successful outcomes of lung adenocarcinoma treated with epithelial growth factor receptor-tyrosine kinase inhibitor (3, 4), bronchoscopy is becoming important for the early diagnosis of lung cancer.

Flexible fiberoptic bronchoscopy (FFB) has been used for more than three decades to diagnose PPLs. In general, PPLs with a diameter of less than 20 mm are categorized as small

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Table 1. **The Characteristics of 115 PPLs**

Median age (range)		64:(19-86)	
Sex	Male/Female	73/42	
Lesion location	Upper	64	(55.6%)
	Middle + Lingular	10	(8.7%)
	Lower	41	(35.7%)
Diagnoses	Malignant	63	(54.8%)
	Benign	52	(45.2%)
Approach	Easy	24	(20.9%)
	Difficult	91	(79.1%)
Bronchoscope	Standard	102	(88.7%)
	Thin	13	(11.3%)
Devices	Standard forceps	85	(74.0%)
	STAF	45	(39.1%)
	Brushing, Curettage	76	(66.1%)
	TBAC	11	(9.7%)
Median times of TBB (range)		3	(0-10)
Use of hemostatic agent		8	(7.0%)
Under sedation		23	(20.0%)
Skill	Excellent	59	(51.3%)
	Other	56	(48.7%)

TBB: Transbronchial biopsy, STAF: Sasada transbronchial angled forceps, TBAC: Transbronchial needle aspiration cytology

lesions (5). Most PPLs with a diameter of 15-20 mm can be easily visualized by fluoroscopy and are considered relatively easy to diagnose through new technology such as endobronchial ultrasonography with a guide sheath (EBUS-GS) or its combination with a virtual bronchoscopic navigation (VBN) system (6-10). EBUS enables the detection of PPLs, thus possibly improving the diagnostic rate (8, 9); furthermore, by using a VBN system, chest physicians can presume the location of PPLs and insert the bronchoscope into the affected bronchus with great certainty (6, 7). However, the accuracy for detecting PPLs smaller than 15 mm has not been evaluated; it can be influenced by bronchoscopic factors such as lesion area, angle of approach, kind of device, or operator skill.

To evaluate the accuracy of new diagnostic technology, the data obtained by the advanced technique should be compared with that obtained by the conventional diagnostic procedures (CDPs). The purpose of this study was to assess the accuracy of the CDPs for detecting PPLs smaller than 15 mm and to evaluate the factors contributing to a successful diagnosis.

Methods

Bronchoscopy was performed for the first time on 115 consecutive patients with a PPL of $\leq$15 mm diameter through chest CT between August 2003 and December 2006 at the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Japan. In some cases, the final diagnosis decision was made by operation and re-examination using bronchoscope. The institutional review committee approved the study protocol, conducted in accordance with the tenets of the Declaration of Helsinki, and all the patients gave written informed consent before bronchoscopy.

The longest diameters of all lesions revealed by chest CT were recorded. "Difficult" approach was defined as follows: standard forceps (FB-21C-1; Olympus, Tokyo, Japan) of a bronchoscope could not reach the lesions or could hardly reach them in two or more directions by X-ray fluoroscopy (not C-arm).

The PPLs confirmed by X-ray fluoroscopy were approached with a standard bronchoscope (1T260, 1T240, 1T 200, 1T40, 6-mm outer diameter; Olympus). If a PPL could be easily approached with standard forceps, biopsy and cytological brushing (BC-202D-3010; Olympus) were performed. If any difficulty was encountered in the standard method, Sasada transbronchial angled forceps (STAF) (HBF-2010SH; Machida Endoscope Co., Ltd., Tokyo, Japan) (14) and a thin bronchoscope (P260F, 4-mm outer diameter; Olympus) were used for transbronchial needle aspiration cytology (TBAC) (NA-1C-1; Olympus) and curettage (CC-4 CR-1; Olympus) rather than routinely performing biopsy with standard forceps. These techniques are defined as CDPs. Each specimen was preserved separately and compared for pathological diagnosis. If the standard bronchoscope could not be inserted in the affected bronchus, a thin bronchoscope was used. If extensive bleeding occurred and was uncontrollable with pressure application for five minutes or more, hemostatic agents (carbazochrome and tranexamic acid) were administered intravenously. To control the cough reflex and uneasiness, a sedative (diazepam) was administered.

Bronchoscopy was performed by one of twenty physicians (including residents and endoscopic specialists), and was preferentially performed by a younger doctor. Some specialists evaluated the operator skill on the basis of years of experience, interest in bronchoscopy, and diligence. Excellent operator skill was defined in terms of a specialist qualification in bronchoscopy and weekly participation in bronchoscopic procedures for five years or more.

Positive diagnostic criteria were as follows:

· Malignant lesion: class IV/V lesion by cytology, except for lesions outside the lung; metastatic lesion; negative case which diagnosis did not attach in a lung field but by cytology or biopsy of lymph gland; malignancy by pathology.

· Benign lesion: nonspecific inflammation for more than six months followed by a reduction in lesion size, except for cases under observation.

The analyzed variables were age, gender, lesion area, tissue number, bronchoscope diameter, kind of device, approach, diagnosis, hemostasis, sedation, and operator skill. The R software was used for univariate and multivariate analyses by logistic regression. Only those variables with a p-value less than 0.15 in the univariate analysis were included in the multiple logistic regression analysis (with lesion area, approach, skill, and hemostasis as factors). A p-value less than 0.05 was considered statistically significant.

Results

Table 1 shows the patient characteristics. The study in-

Table 2. **Clinical Diagnosis and Diagnostic Yield of 115 PPLs**

Disease	Number of lesions with Positive findings / Total number of patients	%
Primary lung cancer	39/59	66.1%
Metastatic lung cancer	0/4	0%
Malignant lesions total	39/63	61.9%
Pulmonary tuberculosis	10/14	71.4%
NTM	4/6	66.7%
Nonspecific inflammation	17/20	85.0%
Hamartoma	2/4	50%
Pneumoconiosis	2/2	100%
Fungus infection	1/4	33%
Others (Amyloidosis)	0/2	0%
Benign lesions total	36/52	69.2%
All lesions total	75/115	65.2%

NTM: Nontuberculous mycobactelial infection

Table 3a. **Diagnostic Factors for Small (≤15 Mm) PPLs: An Univariate Analysis of 115 PPLs**

Variables		Success (n=75)	(%)	Failure (n=40)	p value
Age	≦ 64	42	(70)	18	0.262
	>64	33	(60)	22	
Sex	Male	51	(70)	22	0.170
	Female	24	(60))	18	
Lesion location	Upper	45	(70)	19	
	Middle+Lingular	7	(70)	3	0.128
	Lower	23	(56)	18	
Diagnoses	Malignant	39	(62)	24	0.412
	Benign	36	(69)	16	
Approach	Ease	21	(86)	3	0.016
	Difficult	54	(59)	37	

cluded 73 men and 42 women. Their median age was 64 years (range, 19-86 years). The median longest diameter of the PPLs was 13 mm (range, 5-15 mm). The lesions were mostly located in the upper lobes (55.6%), and 54.8% of the PPLs were malignant. The approach to the PPLs was difficult in almost 80% of the cases, because of the very small lesions. A thin bronchoscope was used in only 11.3% of the cases. STAF and TBAC were applied in 39.1% and 9.7% of the cases, respectively. Transbronchial biopsy (TBB) was generally performed thrice (range, 0-10). The hemostatic agents and sedative were administered in 7% and 20% of the cases, respectively. About 59 PPLs were retrieved under excellent operator skill.

Table 2 shows the pathological findings and diagnostic yields in the study. The overall diagnostic yield was 65.2%, and the yields of the malignant and benign lesions were 61.9% and 69.2%, respectively. Especially, the diagnostic yield of primary lung cancer was 66.1% but that of metastatic lung cancer was 0%.

In the univariate analysis (Table 3a, b), the angle of approach showed a significant difference (p=0.016). Further, the use of a hemostatic agent during bronchoscopy (p=0.10) and operator skill (p=0.078) tended to influence the diagnosis. Although not significant, the lower lobe lesions had a lower diagnostic rate than the other areas.

Next, the factors considered to influence the diagnosis in the univariate analysis were included in the multivariate analysis (Table 4). Again, approach was statistically significant (p=0.019). The lower lobe lesions obviously had a lower diagnostic rate than the other areas. Operator skill and the use of a hemostatic agent were not important for a successful diagnosis in the multivariate analysis.

Discussion

TBB with FFB has been widely used since the 1970s and is now the most common method for retrieving lung tissue (11, 12). In difficult cases, CT-guided needle biopsy (CTGNB) or video-assisted thoracic surgery (VATS) is used (13, 14). However, CTGNB is more invasive than bronchoscopy and results in critical complications, including air embolism and pleural dissemination (15, 16), and VATS is generally not performed in patients with a poor performance status or in the elderly. Therefore, TBB with FFB is still the first choice to diagnose PPLs, and diagnostic procedures including bronchoscopy with STAF (17), broncho-

Table 3b. **Diagnostic Factors for Small (≤15 Mm) PPLs: An Univariate Analysis of 115 PPLs**

Variables		No. of positive samples /Total No.	(%)	p value
Bronchoscope	Standard	68/102	(67)	0.365
	Thin	7/13	(54)	
Devices	TBB, B, C only	42/61	(69)	0.385
	With STAF, TBAC	33/54	(61)	
	STAF only	31/45	(69)	
Tissue Number	<3	30/49	(61)	0.439
	≧3	45/66	(68)	
Hemostasis	Yes	3/8	(36)	0.10
	No	72/107	(67)	
Sedation	Yes	16/23	(70)	0.625
	No	59/92	(64)	
Operator skill	Excellent	43/59	(73)	0.078
	Other	32/56	(57)	

TBB: Transbronchial biopsy, B: Brushing, C: Curettage
STAF: Sasada transbronchial angled forceps, TBAC: Transbronchial needle aspiration cytology

Table 4. **Diagnostic Factors of Standard Bronchoscopy for Small (≤15 Mm) PPLs: A Multivariate Analysis of 115 PPLs**

Variables		No. of positive samples /Total No.	(%)	p value
Lesion location	not Lower	52/74	70.3	0.068
	Lower	23/41	59.1	
Approach	Easy	21/24	87.5	0.019
	Difficult	54/91	59.3	
Operator Skill	Excellent	43/59	72.9	0.117
	Other	32/56	57.1	
Hemostasis	No	72/107	67.3	0.154
	Yes	3/8	37.5	

scopy with an (ultra)thin bronchoscope coupled with a VBN system, and EBUS-GS (6-10) have been developed to complement this technique.

In particular, it is not easy to diagnose small PPLs by bronchoscopy. The *American College of Chest Physicians* does not recommend bronchoscopy for diagnosing PPLs with a diameter of 20 mm or less (5). However, PPLs smaller than 20 mm are being diagnosed comparatively more easily and often, possibly due to developments in technology; therefore, in the present study, the accuracy of bronchoscopic diagnosis of PPLs smaller than 15 mm was evaluated. The approach to the PPLs (≤15 mm) was the most important diagnostic factor; STAF and TBAC can improve the approach to PPLs, are inexpensive, and are easily introducible in institutions (17-19).

Fluoroscopic localization of lesions in the lower lobe basal segments or upper lobe apical segment was the most difficult in the past (20, 21). In the present study, the lower lobe lesions had a lower diagnostic rate than the other areas. PPLs of the lower lobe are difficult to diagnose under fluoroscopy because of overlap of the pericardium and diaphragm or respiratory fluctuation. In such cases, EBUS-GS and a VBN system useful to improve the accuracy of diagnosis. On the other hand, although apical lesions are difficult to diagnose, the use of bronchoscopes with an outer diameter less than 4 mm could overcome the problem. In addition, thin bronchoscopes are preferred in the case of bronchial brushing or TBAC, which involve less bleeding, because the detection of small PPLs under fluoroscopy is difficult after repetitive forceps biopsy and the subsequent bleeding. Operator skill and use of a hemostatic agent tended to have a positive influence on the diagnosis in this study. These factors are essential for a successful diagnosis by reducing the diagnostic time and improving visibility.

In conclusion, the approach to the lesion is the most significant factor influencing the diagnostic accuracy of PPLs smaller than 15 mm. Although the diagnosis of small PPLs has long been a challenge for chest physicians, the introduction of navigable technology such as EBUS-GS or a VBN system may improve the diagnostic accuracy in bronchoscopy.

The authors state that they have no Conflict of Interest (COI).

References

1. Spiro SG, Porter JC. Lung cancer-where are we today? Current advances in staging and nonsurgical treatment. Am J Respir Crit Care Med **166**: 1166-1196, 2002.
2. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology **201**: 798-802, 1996.
3. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med **362**: 2380-2388, 2010.
4. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG 3405): an open label, randomised phase 3 trial. Lancet Oncol **11**: 121-128, 2010.

5. Rivera MP, Mehta AC; American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest **132**: 131S-148S, 2007.
6. Asahina H, Yamazaki K, Onodera Y, et al. Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. Chest **128**: 1761-1765, 2005.
7. Asano F, Matsuno Y, Shinagawa N, et al. A virtual bronchoscopic navigation system for pulmonary peripheral lesions. Chest **130**: 559-566, 2006.
8. Kurimoto N, Miyazawa T, Okimasa S, et al. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest **126**: 959-965, 2004.
9. Paone G, Nicastri E, Lucantoni G, et al. Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. Chest **128**: 3551-3557, 2005.
10. Gildea TR, Mazzone PJ, Karnak D, Meziane M, Mehta AC. Electromagnetic navigation diagnostic bronchoscopy: a prospective study. Am J Respir Crit Care Med **174**: 982-989, 2006.
11. Zavala DC. Diagnostic fiberoptic bronchoscopy: techniques and results of biopsy in 600 patients. Chest **68**: 12-19, 1975.
12. Mitchell DM, Emerson CJ, Collins JV, Stableforth DE. Transbronchial lung biopsy with the fibreoptic bronchoscope: analysis of results in 433 patients. Br J Dis Chest **75**: 258-262, 1981.
13. Tsukada H, Satou T, Iwashima A, Souma T. Diagnostic accuracy of CT-guided automated needle biopsy of lung nodules. AJR Am J Roentgenol **175**: 239-243, 2000.
14. Savage C, Morrison RJ, Zwischenberger JB. Bronchoscopic diagnosis and staging of lung cancer. Chest Surg Clin N Am **11**: 701-721, 2001.
15. Aberle DR, Gamsu G, Goldman JA. Fatal systemic arterial air embolism following lung needle aspiration. Radiology **165**: 351-353, 1987.
16. Seyfer AE, Walsh DS, Graeber GM, Nuno IN, Eliasson AH. Chest wall implantation of lung cancer after thin-needle aspiration biopsy. Ann Thorac Surg **48**: 284-286, 1989.
17. Sasada S, Ogata Y, Kobayashi M, et al. Angled forceps used for transbronchial biopsy in which standard forceps are difficult to manipulate: a comparative study. Chest **129**: 725-733, 2006.
18. Shure D. Transbronchial biopsy and needle aspiration. Chest **95**: 1130-1138, 1989.
19. Reichenberger F, Weber J, Tamm M, et al. The value of transbronchial needle aspiration in the diagnosis of peripheral pulmonary lesions. Chest **116**: 704-708, 1999.
20. Checani V. Bronchoscopic diagnosis of solitary pulmonary nodules and lung masses in the absence of endobronchial abnormality. Chest **109**: 620-625, 1996.
21. Baaklini WA, Reinoso MA, Gorin AB, Sharafkaneh A, Manian P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Chest **117**: 1049-1054, 2000.

Invest New Drugs
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PHASE I STUDIES

Safety and pharmacokinetic study of *nab*-paclitaxel plus carboplatin in chemotherapy-naïve patients with advanced non–small cell lung cancer

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Summary *Background* Nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) is a Cremophor EL–free formulation of paclitaxel newly designed to avoid solvent-related toxicities. We have evaluated the safety, tolerability, pharmacokinetics, and tumor response profile of weekly *nab*-paclitaxel (100 mg/m^2) infusion together with administration of carboplatin at an area under the curve (AUC) of 6 every 3 weeks in Japanese patients with advanced non–small cell lung cancer (NSCLC). *Methods* *Nab*-paclitaxel (100 mg/m^2) was administered without steroid or antihistamine premedication as a 30-min intravenous infusion once a week in combination with carboplatin at an AUC of 6 on day 1 of repeated 21-day cycles. The pharmacokinetics of both drugs were analyzed, and both adverse events and treatment response were monitored. *Results* Eighteen patients were enrolled in the study. The most frequent treatment-related toxicities of grade 3 or 4 were neutropenia (67%), leukopenia (50%), and anemia (22%). No severe hypersensitivity reactions were observed despite the lack of premedication, and no unexpected or new toxicities were detected. Pharmacokinetics analysis did not reveal any substantial drug-drug interactions. Seven partial responses were observed among the 18 evaluable patients, yielding a treatment response rate of 38.9%. *Conclusions* The combination of *nab*-paclitaxel (100 mg/m^2) administered weekly and carboplatin at an AUC of 6 every 3 weeks was well tolerated in Japanese patients with advanced NSCLC. This combination therapy also showed promising antitumor activity and was not associated with relevant pharmacokinetic interactions.

Keywords *Nab*-paclitaxel · Carboplatin · Non–small cell lung cancer · Pharmacokinetics · Safety

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Introduction

Lung cancer is the leading cause of death related to cancer worldwide, with non–small cell lung cancer (NSCLC) accounting for 85% of lung cancer cases [1]. Platinum-based chemotherapy is the mainstay of first-line treatment for advanced NSCLC on the basis of the moderate improvement in survival and quality of life it confers compared with best supportive care alone [2]. Given the safety and efficacy limitations of current therapeutic options, however, new chemotherapeutic agents and combi-

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nation regimens are needed to further ameliorate symptoms and increase antitumor activity in a manner that is both convenient and safe in patients with advanced NSCLC.

The most commonly used taxane combination regimen for treatment of advanced NSCLC is carboplatin plus solvent-based paclitaxel. Paclitaxel is highly hydrophobic, and first-generation formulations include Cremophor EL (polyoxyethylated castor oil) and an ethanol vehicle to allow parenteral administration [3]. Given that Cremophor EL causes leaching of the plasticizers from standard intravenous tubing and is also associated with hypersensitivity reactions, administration of solvent-based paclitaxel requires a long infusion period (typically 3 h), the use of special non–polyvinyl chloride infusion systems and in-line filtration, and premedication with corticosteroids, diphenhydramine, and an H_2 histamine receptor antagonist to minimize the incidence of potentially life-threatening hypersensitivity [4, 5]. Severe and sometimes fatal hypersensitivity reactions sometimes still occur, however, even after administration of these premedications [6].

Nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel, Abraxane) was developed for delivery of paclitaxel as a suspension of albumin particles in saline, allowing a shorter infusion time and use of a standard infusion set [7]. This new Cremophor EL–free formulation does not require steroid and antihistamine premedication to prevent hypersensitivity reactions. Furthermore, preclinical studies have suggested that this formulation may improve drug delivery into tumors [8]. In phase I trials, *nab*-paclitaxel has been administered safely at doses higher than labeled doses for solvent-based paclitaxel [7]. A phase III trial in patients with advanced breast cancer showed that administration of *nab*-paclitaxel every 3 weeks (q3w) resulted in a significantly higher response rate (33 versus 19%, $P<0.001$) and longer time to tumor progression (5.8 versus 4.2 months, $P<0.006$) compared with q3w solvent-based paclitaxel [9]. A phase II study of *nab*-paclitaxel at 260 mg/m^2 q3w in chemotherapy-naïve patients with advanced NSCLC also revealed single-agent antitumor activity with a response rate of 16% [10]. Furthermore, weekly administration of *nab*-paclitaxel (125 mg/m^2) yielded an increased response rate of 30% in 40 individuals with advanced NSCLC who had not received prior chemotherapy [11]. More recently, a dose-finding phase II study demonstrated that *nab*-paclitaxel administered weekly was associated with less serious adverse events when administered q3w, with significant reductions in the incidence of peripheral neuropathy, myalgia, arthralgia, and alopecia [12]. In the phase II study, weekly administration of *nab*-paclitaxel at 100 mg/m^2 combined with carboplatin (area under the curve [AUC], 6) yielded a response rate of 48% and median progression-free survival of 6.2 months as first-line treatment for advanced NSCLC [12]. Given the promising efficacy and excellent safety of *nab*-paclitaxel, the combination of weekly *nab*-paclitaxel with carboplatin warrants further investigation. To date, however, pharmacokinetic data for such treatment have been limited. The primary objective in the present study was to evaluate the safety of weekly *nab*-paclitaxel (100 mg/m^2) administered in combination with q3w carboplatin at an AUC of 6 in Japanese advanced NSCLC without prior systemic chemotherapy. The secondary objectives were to determine the pharmacokinetics of paclitaxel after *nab*-paclitaxel administration on cycle 1 days 1 (with carboplatin) and 15 (without carboplatin).

Patients and methods

Patients

Eligible patients were 18 years of age or older with histologically or cytologically confirmed NSCLC of stage IIIB or IV. They were required to be naïve with regard to chemotherapy for metastatic disease. The eligibility criteria also included adequate bone marrow, hepatic, and renal function, an Eastern Cooperative Oncology Group performance status of 0 or 1, a life expectancy of >12 weeks, and radiologically documented measurable disease. Individuals were excluded if they had evidence of active brain metastasis or preexisting peripheral neuropathy of grade ≥2 defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0, or if they had received radiotherapy in the previous 4 weeks. Patients with any other clinically serious concurrent illness were also excluded.

The study followed the ethical principles in the Declaration of Helsinki, and the study protocol was approved by the institutional review board of each participating center. All patients received information regarding the nature and purpose of the study, and they provided written informed consent before study-related procedures were performed.

Treatment

The study was conducted to evaluate the safety, tolerability, pharmacokinetics, and tumor response profile of weekly *nab*-paclitaxel at 100 mg/m^2 and q3w carboplatin at an AUC of 6 in Japanese patients with advanced NSCLC. Carboplatin was administered at an AUC of 6 calculated according to the Calvert formula on day 1 of a 21-day cycle. *Nab*-paclitaxel (100 mg/m^2) was administered by a 30-min intravenous infusion on days 1, 8, and 15 of each cycle without steroid or antihistamine premedication to prevent a hypersensitivity reaction. On days of carboplatin dosing, patients received the serotonin/5-hydroxytryptamine receptor 3 (5-HT_3) antagonist as antiemetic therapy. A

maximum of two dose reductions was allowed for defined adverse events of grade 3 or 4; the minimum dose for *nab*-paclitaxel was 50 mg/m^2 and that for carboplatin was an AUC of 3. All patients underwent comprehensive baseline assessments including clinical laboratory tests and imaging studies. Patients also received follow-up assessments and monitoring at regular intervals. Toxicity evaluations were based on CTCAE v3.0. Objective response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Pharmacokinetics

Blood samples were collected on days 1 and 15 of cycle 1 (before as well as 0.5, 1, 1.5, 2, 4, 6, 8, 24, 48, and 72 h after dosing of *nab*-paclitaxel; before as well as 0.5, 1.0, 1.5, 3.5, 5.5, 7.5, and 23.5 h after dosing of carboplatin) and centrifuged, and the plasma supernatants were stored at −20°C until analysis. The plasma concentration of paclitaxel was measured by validated high-performance liquid chromatography and tandem mass spectrometry, with the lower limit of quantification being 1.00 ng/mL. The plasma concentration of free platinum derived from carboplatin was determined by validated inductively coupled plasma mass spectrometry, with the lower limit of quantification also being 1.00 ng/mL.

The maximum observed concentration (C_{max}) was determined directly from the observed plasma concentrations. The apparent terminal elimination rate constant (λz) was estimated by linear regression analysis of the decline from individual plasma concentration–time data. At least three points that resulted in the highest correlation coefficient were used for the λz calculation. The terminal elimination half-life ($t_{1/2}$) was calculated as $t_{1/2}=\ln(2)/\lambda z$ for each patient. The area under the plasma concentration–time curve from time 0 to the last measurable time (AUC_{0-t}) was calculated by the trapezoidal method. Individual AUCs extrapolated to infinity (AUC_{inf}) were calculated from the last measurable concentration (C_{last}) according to the formula $AUC_{inf}=AUC_{0-t}+C_{last}/\lambda z$. Individual area under the plasma concentration–time curves for free platinum were estimated from the concentration data. All pharmacokinetic parameters for paclitaxel and free platinum were calculated by noncompartmental techniques with the use of WinNonlin software (Professional Network version 5.2; Pharsight, Mountain View, CA).

Results

Patients

Eighteen chemotherapy-naïve patients with advanced NSCLC were enrolled in the study (Table 1). Four patients were female and 14 were male, and the median age was 64 years (range, 37 to 72). Histological analysis revealed that 14 patients had adenocarcinoma and three had squamous cell carcinoma; one patient who had unspecified NSCLC was classified as "other."

Table 1 Characteristics of the study patients

Number of patients	18
Median age, years (range)	64 (37–72)
Sex	
Male	14
Female	4
Performance status	
0	9
1	9
Disease stage	
IIIB	1
IV	17
Histology	
Adenocarcinoma	14
Squamous cell carcinoma	3
Other	1

Treatment delivery and safety

All 18 enrolled patients received at least one dose of the study treatment. A total of 82 cycles of treatment was delivered overall, with a median number of cycles per patient of 4 (range, 1 to 11). Dose reductions stipulated by the study protocol were instituted in 12 patients, mainly as

Table 2 Treatment-related toxicities

Adverse event	Toxicity grade			
	1	2	3	4
Hematologic				
Neutropenia	1	4	8	4
Anemia	3	9	4	0
Thrombocytopenia	5	6	0	0
Leukopenia	3	4	8	1
Nonhematologic				
Anorexia	4	5	3	0
Nausea	5	3	1	0
Vomiting	3	3	0	0
Fatigue	9	3	0	0
Arthralgia	8	1	0	0
Myalgia	10	1	0	0
Neuropathy: sensory	9	0	1	0
Alopecia	14	4	–	–
Febrile neutropenia	–	–	2	0

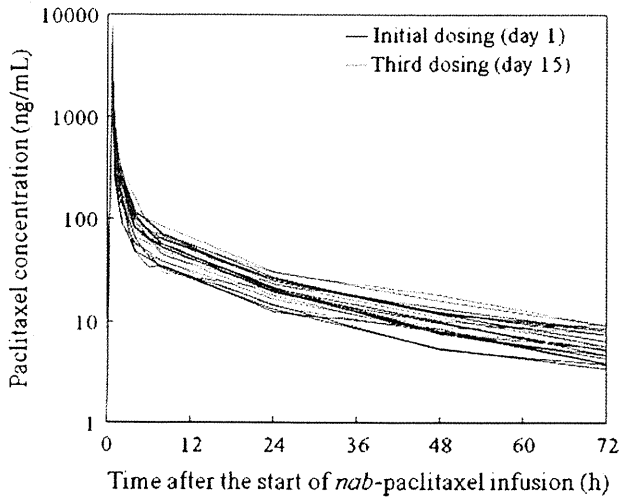

Fig. 1 Individual plasma paclitaxel concentration–time profiles for the initial (day 1) and third (day 15) dosings of *nab*-paclitaxel

a result of the development of neutropenia. The most common reason for treatment discontinuation was disease progression. Treatment was withdrawn because of adverse events (neuropathy or neutropenia) in two patients. All patients were evaluable for safety analysis. The major adverse events during the entire treatment period are shown in Table 2. Hematologic adverse events of grade ≥3 included neutropenia (67%), leukopenia (50%), and anemia (22%), with neutropenia of grade 4 being observed in four patients and leukopenia of grade 4 in one patient. In 12 patients with grade 3 or 4 neutropenia, the median time to neutrophil nadirs was 15 days and the median time from nadir to attaining recovery neutrophil level of 1500/mm^3 or more was 11 days. Nonhematologic toxicities of grade ≥3 included anorexia (17%), febrile neutropenia (11%), nausea (6%), and sensory neuropathy (6%). There were no treatment-related deaths. The adverse events observed in the present study were predictable from the safety profiles of *nab*-paclitaxel and carboplatin, and all events were well managed.

Pharmacokinetics

Twelve and nine patients were evaluable for paclitaxel pharmacokinetics analysis for the initial dosing of *nab*-paclitaxel administered with carboplatin (day 1 of cycle 1) and for the third dosing of *nab*-paclitaxel alone (day 15 of cycle 1), respectively. The individual paclitaxel concentration–time profiles are shown in Fig. 1. Paclitaxel pharmacokinetic profiles showed a multiphasic elimination and appeared similar for the initial and third dosings. A trace level of paclitaxel was detected in the trough samples obtained before the third dosing (Fig. 1), suggesting that paclitaxel accumulates in plasma after repeated administration of *nab*-paclitaxel (on days 1, 8, and 15). The C_{max}, AUC_{0-t}, AUC_{inf}, and $t_{1/2}$ values for paclitaxel were all ~20% higher after the third dosing (day 15) of *nab*-paclitaxel compared with those after the initial dosing on day 1 (Table 3).

Pharmacokinetic parameters for carboplatin were calculated from the free platinum concentration after the initial dosing of carboplatin following that of *nab*-paclitaxel (Table 3). The free platinum concentration–time profiles showed monophasic elimination with a $t_{1/2}$ of ~4 h. The C_{max} and AUC_{inf} for free platinum were 23,903 ng/mL and 3.89 mg·min/mL, respectively.

Tumor response

All 18 enrolled patients were evaluable for response. There were seven partial responses and no complete responses, yielding an overall response rate of 38.9% (95% confidence interval, 17.3 to 64.3).

Table 3 Pharmacokinetic parameters for paclitaxel and free platinum in plasma

Parameter		Initial dosing (day 1)		Third dosing (day 15)	
		Mean	SD	Mean	SD
Paclitaxel					
C_{max}	(ng/mL)	3460	905	4443	1827
AUC_{0-t}	(ng·h/mL)	3893	897	4565	1346
AUC_{inf}	(ng·h/mL)	4073	929	5060	1325
$t_{1/2}$	(h)	24.2	3.02	29.5	3.18
CL	(L/h/ m^2)	25.9	6.61	21.0	5.51
Vz	(L/m^2)	913	292	897	269
Free platinum					
C_{max}	(ng/mL)	23,903	3901		
AUC_{0-t}	(mg·min/mL)	3.86	0.35		
AUC_{inf}	(mg·min/mL)	3.89	0.36		
$t_{1/2}$	(h)	3.97	0.21		

CL total clearance; *Vz* volume of distribution

Discussion

We have evaluated the feasibility of administering *nab*-paclitaxel (100 mg/m^2) weekly as a 30-min uninterrupted intravenous infusion combined with q3w IV administration of carboplatin at an AUC of 6 in Japanese patients with advanced NSCLC. We found that this combination could be safely administered without steroid and antihistamine premedication to prevent the development of hypersensitivity reactions. With regard to nonhematologic toxicities, sensory neuropathy, arthralgia, and myalgia of grade 2 or 3 were each observed in only one patient (5.6%). These results compare favorably with the toxicity profiles described for the standard combination of carboplatin plus solvent-based paclitaxel in previous studies with NSCLC patients, in which higher frequencies (~20%) of sensory neuropathy, arthralgia, and myalgia of grade 2 or 3 were observed [13]. Our findings thus support the notion that *nab*-paclitaxel, a Cremophor EL–free formulation of paclitaxel, has an improved toxicity profile compared with that of conventional paclitaxel formulated with Cremophor EL. This difference in toxicity profiles is important because such toxicities can be debilitating in patients for whom symptom palliation is the primary therapeutic goal.

Although no effect of the sequence of *nab*-paclitaxel and carboplatin administration on the pharmacokinetics of paclitaxel has been described previously [14]. possible interactions of *nab*-paclitaxel and concomitantly administered carboplatin have not been specifically investigated. In the present study, the effect of carboplatin coadministration on the pharmacokinetics of paclitaxel was examined in similar patients treated with carboplatin and weekly *nab*-paclitaxel. The pharmacokinetic parameters of paclitaxel after *nab*-paclitaxel administration with or without carboplatin were similar to those described after single administration of *nab*-paclitaxel at 100 mg/m^2 in a previous study [7]. Whereas the AUC and C_{max} values of paclitaxel were increased ~20% after the third dosing (day 15) of *nab*-paclitaxel compared with those after the first dosing, these increases were likely due to the accumulation of paclitaxel after repeated *nab*-paclitaxel administration because a trace level of paclitaxel in plasma was detected immediately before the third dosing of *nab*-paclitaxel. The pharmacokinetics of carboplatin revealed that the AUC_{inf} calculated from the free platinum concentration was 3.89±0.36 mg·min/mL, corresponding to a range of 24.5 to 45.3% below the target AUC of 6. This finding is consistent with previous results showing that the measured AUC of carboplatin was 30% lower than the target AUC when a modified Calvert formula with creatinine clearance was substituted for glomerular filtration rate [15, 16]. Together, the present data suggest that concomitant administration of *nab*-paclitaxel and carboplatin according to the selected treatment schedule had no substantial impact on the pharmacokinetics of either drug. However, pharmacokinetic findings remain to be verified in a crossover study designed to examine drug-drug interactions.

The physical nature of the Cremophor EL–paclitaxel suspension may limit access of paclitaxel to tumor cells. Preclinical studies have shown that the Cremophor EL–free formulation of paclitaxel (*nab*-paclitaxel) yielded higher intratumoral levels of paclitaxel, as a result of albumin transportation into tumor cells, as well as higher antitumor activity [7, 8]. Although tumor evaluation was not the primary objective of the present study and the small sample size precluded any definitive conclusion regarding treatment efficacy, the combination of *nab*-paclitaxel and carboplatin yielded promising results, with seven partial responses observed among the 18 evaluable patients, for a response rate of 38.9%. A previous study of patients with advanced NSCLC showed that first-line treatment with weekly *nab*-paclitaxel (100 mg/m^2) plus carboplatin (according to the same schedule as that in the present study) similarly obtained a response rate of 48% (95% confidence interval, 28 to 68) [12]. Given its favorable safety profile and promising antitumor activity, this drug combination is currently under evaluation in a large randomized phase III trial (n=1050) in comparison with a standard dose of solvent-based paclitaxel plus carboplatin.

In conclusion, *nab*-paclitaxel administered weekly at 100 mg/m^2 in combination with carboplatin given q3w at an AUC of 6 was found to be well tolerated in Japanese patients with advanced NSCLC. No clinically relevant pharmacokinetic interaction of the two therapeutic agents was detected, and the observed antitumor activity merits further clinical investigation.

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Conflicts of interest H. Yamaya, K. Ono have been full-time employees of Taiho Pharmaceutical Co. Ltd.

References

1. Jemal A, Siegel R, Xu J et al (2010) Cancer statistics, 2010. CA Cancer J Clin 60:277–300
2. Azzoli CG, Baker S Jr, Temin S et al (2009) American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 27:6251–6266
3. Rowinsky EK, Cazenave LA, Donehower RC (1990) Taxol: a novel investigational antimicrotubule agent. J Natl Cancer Inst 82:1247–1259
4. Weiss RB, Donehower RC, Wiernik PH et al (1990) Hypersensitivity reactions from taxol. J Clin Oncol 8:1263–1268

5. Gelderblom H, Verweij J, Nooter K et al (2001) Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer 37:1590–1598
6. Kloover JS, den Bakker MA, Gelderblom H et al (2004) Fatal outcome of a hypersensitivity reaction to paclitaxel: a critical review of premedication regimens. Br J Cancer 90:304–305
7. Nyman DW, Campbell KJ, Hersh E et al (2005) Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. J Clin Oncol 23:7785–7793
8. Sparreboom A, van Zuylen L, Brouwer E et al (1999) Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. Cancer Res 59:1454–1457
9. Gradishar WJ, Tjulandin S, Davidson N et al (2005) Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 23:7794–7803
10. Green MR, Manikhas GM, Orlov S et al (2006) Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol 17:1263–1268
11. Rizvi NA, Riely GJ, Azzoli CG et al (2008) Phase I/II trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non-small-cell lung cancer. J Clin Oncol 26:639–643
12. Socinski MA, Manikhas GM, Stroyakovsky DL et al (2010) A dose finding study of weekly and every-3-week nab-Paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer. J Thorac Oncol 5:852–861
13. Ohe Y, Ohashi Y, Kubota K et al (2007) Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 18:317–323
14. Stinchcombe TE, Socinski MA, Walko CM et al (2007) Phase I and pharmacokinetic trial of carboplatin and albumin-bound paclitaxel, ABI-007 (Abraxane) on three treatment schedules in patients solid tumors. Cancer Chemother Pharmacol 60:759–766
15. Huizing MT, van Warmerdam LJ, Rosing H et al (1997) Phase I and pharmacologic study of the combination paclitaxel and carboplatin as first-line chemotherapy in stage III and IV ovarian cancer. J Clin Oncol 15:1953–1964
16. Calvert AH, Egorin MJ (2002) Carboplatin dosing formulae: gender bias and the use of creatinine-based methodologies. Eur J Cancer 38:11–16

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CLINICAL INVESTIGATION

PHASE I RESULTS OF VINORELBINE WITH CONCURRENT RADIOTHERAPY IN ELDERLY PATIENTS WITH UNRESECTABLE, LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER: WEST JAPAN THORACIC ONCOLOGY GROUP (WJTOG3005-DI)

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Purpose: To investigate the safety and efficacy of concurrent vinorelbine and thoracic radiotherapy in elderly patients with locally advanced non–small-cell lung cancer (NSCLC).

Methods and Materials: Eligible patients were 71 years of age or older with unresectable Stage III NSCLC. Patients were treated with thoracic radiotherapy (60 Gy) and concurrent vinorelbine (20 mg/m^2 in Level 1 and 25 mg/m^2 in Level 2) on Days 1 and 8 every 3 weeks for two cycles, followed by adjuvant vinorelbine (25 mg/m^2) on Days 1 and 8 every 3 weeks for two cycles.

Results: Four patients were enrolled at Level 1. One patient experienced Grade 3 febrile neutropenia at Level 1 and the dose was escalated to Level 2. At Level 2, 2 of 6 patients experienced dose-limiting toxicities (Grade 4 neutropenia in 1 patient and Grade 3 infection in another). Three of 6 patients developed late Grade 2 or 3 pneumonitis. Therefore, the dose was de-escalated to Level 1. An additional 6 patients were enrolled at Level 1, 4 of whom experienced dose-limiting toxicities (incomplete radiotherapy because of Grade 2 pneumonitis in 1 patient and Grade 3 infection in 1, Grade 3 febrile neutropenia in 1, and Grade 3 esophagitis in 1). Moreover, late Grade 3 pneumothorax and Grade 5 pneumonitis occurred in 1 and 1 patient, respectively. Overall, Grade 2, 3 and 5 pneumonitis occurred in 3, 3, and 1 among 16 patients, respectively.

Conclusions: Concurrent vinorelbine and thoracic radiotherapy resulted in a high incidence of severe pneumonitis when the standard dose of this agent was used for elderly patients. We therefore recommend caution in the use of this regimen and schedule for elderly patients.

Elderly, NSCLC, Chemo-radiation, Phase I, Pneumonitis.

INTRODUCTION

As a result of increasing life expectancy, the incidence of lung cancer in elderly patients is rising (1). For elderly patients, there is an increased incidence of age-related physiological changes, which increase the risk of toxicity related to anticancer treatment. Although elderly patients should be treated based on evidence-based clinical recommendations, it is difficult to do so because these are usually underrepresented in clinical trials. Concurrent chemoradiation has become standard care for good performance status patients with unresectable Stage IIIA/B non–small-cell lung cancer (NSCLC) (2). There are two possible advantages of concurrent chemotherapy. One is the radiosensitizing effect of chemotherapy; the other is the eradication of micrometastases. Therefore, full-dose chemotherapy (3, 4) concurrent with thoracic radiotherapy is the standard of care for chemo-radiation in younger patients because these agents are expected to suppress micrometastases and to enhance the cytotoxic effects of irradiation. However, it is still unclear whether combined full-dose chemotherapy and radiotherapy is also suitable for elderly patients, and thoracic radiotherapy alone is standard for elderly patients with locally advanced NSCLC (5).

For elderly patients with metastatic NSCLCs, the Elderly Lung Cancer Vinorelbine Italian Study (6) showed that vinorelbine is significantly superior in regard to survival than the best supportive care alone. The Multicenter Italian Lung Cancer in the Elderly Study (7) reported that a combination of vinorelbine plus gemcitabine is not more effective

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than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC. From these results, single-agent vinorelbine is considered the standard care for disseminated NSCLC in elderly patients.

In an *in vitro* study, because vinorelbine showed radiosensitization (8), single-agent vinorelbine combined with thoracic radiotherapy could be applied with the goal of increasing locoregional control, while also contributing to the eradication of presumed microscopic disseminated disease for elderly patients with Stage III NSCLC. From reported clinical studies, single-agent vinorelbine plus thoracic radiotherapy (9) or cisplatin and vinorelbine plus thoracic radiotherapy were indicated as feasible for patients with Stage III NSCLC (10–13). The present Phase I study was conducted to investigate the safety and efficacy of concurrent vinorebine and thoracic radiotherapy for elderly patients with locally advanced NSCLC.

METHODS AND MATERIALS

Patient eligibility

Eligible patients were required to meet the following criteria:to have histologically or cytologically proven, unresectable (multi-station N2 disease, insufficient lung function for lobectomy or pneumonectomy), Stage IIIA or IIIB NSCLC as defined by TNM Classification of Malignant Tumors (sixth edition), no previous chemotherapy or radiotherapy, a performance status of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) scale, age of 71 years or more, adequate bone marrow reserve (leukocyte count $\geq$4,000 mm^3, neutrophil count $\geq$2,000/mm^3, platelet count $\geq$100,000/mm^3), normal liver function (total serum bilirubin $\leq$1.5 mg/dl), normal renal function (normal serum creatinine $\leq$1.5 mg/dl), and pulmonary function (PaO_2 $\geq$70 torr). Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, or myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy. Each participating center's institutional review board approved the study, and written informed consent was obtained from all patients.

Clinical study design

This was an open-label, multi-center, single-arm, dose-escalating Phase I study. Vinorelbine was administered at Dose Level 1 (20 mg/m^2 during thoracic radiotherapy and 25 mg/m^2 as consolidation chemotherapy) and Dose Level 2 (25 mg/m^2 during thoracic radiotherapy and 25 mg/m^2 as consolidation chemotherapy). Vinorelbine was administered by bolus intravenous injection on Days 1 and 8. This chemotherapy regimen was repeated every 3 weeks for two cycles during thoracic radiotherapy and two cycles as consolidation chemotherapy.

Radiation therapy was administered using 6- or 10-MV X-rays in 2-Gy fractions five times weekly. All patient treatment plans were designed based on a three-dimensional treatment planning system. The gross tumor volume was delineated according to the primary tumor and nodal involvement determined by computed tomography (CT). The clinical target volume was defined and contoured with 5 to 10 mm around the gross tumor volume and contours around the regional lymph node regions, *i.e.*, the ipsilateral hilum and the mediastinum. Planning Target Volume (PTV) 1 included the clinical target volume plus a 5- to 10-mm margin; PTV 2 included the gross tumor volume plus a 10-mm margin. An additional margin was added if necessary. Beam shaping was performed using a multileaf collimator. The standard of practice was to prescribe 60 Gy to PTV 2 and 40 Gy to PTV 1 with concurrent chemotherapy. Other objectives were to restrict the relative volume of the normal lung irradiation to a dose of >20 Gy (V20) to be 35% or less and the maximum spinal cord dose was restricted to <44 Gy. The dose was prescribed to the isocenter of this point. No tissue heterogeneity correction was performed.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed once a week during the course of concurrent chemoradiation therapy. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (14). Vinorelbine administration on Day 8 was omitted if any of the following toxicities were noted: leukocyte count <2,000/mm^3, platelet count <50,000/mm^3, or any nonhematological toxicity Grade $\geq$3 except for nausea and vomiting. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on Day 1: leukocyte count <3,500/mm^3, platelet count <100,000/mm^3, or any nonhematological toxicity Grade $\geq$3 except for nausea and vomiting. The dose of vinorelbine in the second cycle of consolidation chemotherapy was reduced to 20 mg/m^2, if any of the following toxicities were noted in the first cycle: leukocyte count <1,000 mm^3, platelet count <20,000 mm^3, or any nonhematological toxicity Grade $\geq$3 except for nausea and vomiting.

Doses were escalated according to the frequency of dose-limiting toxicity (DLT) evaluated during the first and second cycles of chemotherapy and thoracic radiatiotherapy. DLT was defined as a neutrophil count <500/mm^3 lasting $\geq$4 days, febrile neutropenia Grade $\geq$3, platelet count <20,000/mm^3, any nonhematological toxicity Grade $\geq$3 other than nausea, vomiting, constipation, or sensory neuropathy, failure to administer vinorelbine at least three times during thoracic radiotherapy and failure to complete thoracic radiotherapy until 8 weeks from the initiation of treatment. At least 3 patients were enrolled at each dose level. If more than one-third of the patients experienced DLTs among the initial patients, 3 more

Table 1. Patient characteristics

Patient no.	Age (y)	Sex	Weight loss	Histology	Brinkman Index*	T stage N stage	Dose level
1	71	M	–	Sq	1120	T3N2	1
2	79	M	–	Ad	960	T4N2	1
3	80	M	–	Sq	1500	T2N2	1
4	71	M	–	Ad	1200	T2N2	1
5	73	F	–	Ad	0	T1N2	2
6	71	M	–	Sq	1920	T4N0	2
7	73	M	–	Ad	1500	T1N3	2
8	76	M	–	Ad	800	T1N2	2
9	72	M	–	Sq	1100	T4N1	2
10	74	M	–	Ad	1040	T2N2	2
11	71	M	+	La	1020	T2N2	1
12	76	M	+	Ad	1220	T2N2	1
13	77	M	–	Ad	810	T3N2	1
14	76	M	–	Ad	510	T4N2	1
15	76	M	–	Sq	600	T2N2	1
16	77	M	Unknown	Ad	3440	T1N3	1

Abbreviations: M = male; F = female; Sq = squamous cell carcinoma; Ad = adenocarcinoma; La = Large cell carcinoma.

* Brinkman Index value is defined as number of cigarettes smoked per day multiplied by smoking years.

Table 2. Treatment delivery

	Dose level 1 (n = 10) n (%)	Dose level 2 (n = 6) n (%)
Total radiotherapy dose (Gy)		
60	8 (80)	6 (100)
50–59	2 (20)	0 (0)
<50	0 (0)	0 (0)
No. of chemotherapy cycles		
During radiotherapy		
2	10 (100)	5 (83)
1	0 (0)	1 (17)
0	0 (0)	0 (0)
Consolidation chemotherapy		
2	5 (50)	1 (17)
1	1 (10)	4 (67)
0	4 (40)	1 (17)

patients were entered at this dose level, and the dose escalation continued to the next level if less than one-half of the patients experienced DLT. The tentative recommended dose (RD) was defined as the level at which DLT was observed in less than 50% of the patients. Once a tentative RD was decided, additional patients were enrolled to make a total of 10 patients at the tentative RD level. Initially, tentative RD was determined on the basis of DLTs occurring during the first and second cycles of chemotherapy and thoracic radiotherapy to add the patients at those levels, and final the RD was determined on the basis of both acute and late toxicities occurring up to 4 weeks after completion of consolidation chemotherapy at the tentative RD level. If less than 50% of patients experienced DLT, that level was considered to be the final RD.

Treatment assessment

Patients were evaluated before treatment with a complete blood cell count, differential count, routine chemistry measurement, chest radiograph, chest CT scan, abdominal CT scan, whole-brain MRI or CT scan, and an isotope bone scan or 18F-fluorodeoxyglucose–positron emission tomography. Evaluations performed weekly were complete blood cell count, differential count, routine chemistry measurements, physical examination, and toxicity assessment. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumor criteria (15). The overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence, confirmed by repeated assessments performed no less than 4 weeks after the criteria for response were first met.

Overall survival has been defined as the time from the date of registration to the date of death or the date of last contact. Progression-free survival has been defined as the time between the date of registration to disease progression or death (whichever occurs first) or the date of last contact.

RESULTS

Between September 2006 and February 2009, 16 patients were enrolled in the trial, all of whom received treatment in the trial. Demographic data are presented in Table 1. The median follow-up time was 17.0 months for all patients and 21.7 months for those patients still alive.

Four patients were started at Level 1. At this dose level, 1 patient (Patient 4) experienced Grade 3 infection on Day 36. Because the infection resolved, thoracic radiotherapy was restarted on Day 46. This patient also experienced Grade 3 pneumonitis after completion of thoracic radiotherapy. Others experienced no DLT. One of 4 patients developed DLT, and the dose was escalated to Level 2.

At Level 2, 3 patients were initially registered. One patient (Patient 6) experienced Grade 4 neutropenia lasting 4 days, and 1 patient (Patient 7) experienced Grade 3 infection on Day 35. Both patients had complete thoracic radiotherapy after resolving these toxicities. Because 2 of 3 patients had

Table 3. Overall toxicities

	Dose level 1 (n = 10), Grade					Dose level 2 (n = 6), Grade				
Toxicity	1	2	3	4	3–4 (%)	1	2	3	4	3–4 (%)
Leukopenia	3	4	2	1	30	0	0	3	2	83
Neutropenia	3	2	1	2	40	0	1	3	1	67
Anemia	3	4	0	0	0	2	4	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0
AST	0	0	0	0	0	0	0	0	0	0
ALT	0	0	0	0	0	2	0	0	0	0
Total bilirubin	0	0	0	0	0	0	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	0	0
Hyponatremia	0	0	0	0	0	0	0	0	0	0
Infection	0	1	2	0	20	0	0	1	0	17
Febrile neutropenia	—	—	2	0	20	—	—	0	0	0
Nausea	1	1	0	0	0	0	2	1	0	17
Diarrhea	1	0	0	0	0	0	0	0	0	0
Stomatitis	0	0	0	0	0	0	0	0	0	0
Esophagitis	2	3	1	0	10	2	2	1	0	17
Dermatitis	7	0	0	0	0	3	2	0	0	0
Sensory neuropathy	0	0	0	0	0	0	0	0	0	0
Pneumonitis	3	2	1	1*	20	0	1	2	0	33
Pneumothorax	0	0	1	0	10	0	0	0	0	0

* Grade 5 toxicity.

Table 4. Dose-limiting toxicities and symptomatic pneumonitis

Toxicity	Dose level 1 (n = 10)			Dose level 2 (n = 6)		
	During RT	Late*	Overall	During RT	Late*	Overall
Neutropenia Grade 4 for >4 days	0	–	0 (0%)	1	–	1 (17%)
Febrile neutropenia Grade ≥3	2	–	2 (20%)	1	–	1 (17%)
Infection Grade ≥3	1	1	2 (20%)	0	0	0 (0%)
Pneumonitis Grade ≥2	2	4	4 (40%)	0	3	3 (50%)
Pneumothorax Grade ≥3	0	1	1 (10%)	0	0	0 (0%)
Esophagitis Grade ≥3	1	0	1 (10%)	0	1	1 (17%)
Total†	5	4	6 (60%)	2	3	5 (83%)

Abbreviation: RT = radiotherapy.
* Late toxicities were observed from completion of RT to at least until 4 weeks after completion of consolidation chemotherapy.
† Because of cases with multiple toxicities, the total can not be obtained by simple addition.

developed DLTs, 3 additional patients were added at this dose level. No DLT developed by the completion of thoracic radiotherapy in these patients. However, Patients 5 and 8 developed Grade 3 pneumonitis 4 weeks and 2 weeks after completion of thoracic radiotherapy respectively, and Patient 10 developed Grade 2 pneumonitis 3 weeks after completion of thoracic radiotherapy. Overall, 3 of 6 patients at Dose Level 2 developed Grade 2 or 3 pneumonitis. The investigators therefore discussed these findings; this dose level was judged to be toxic, and tentative RD was determined as Level 1. To check the safety of Dose Level 1, 6 more patients were added at Dose Level 1.

Among 6 additional patients at Dose Level 1, Patient 12 developed Grade 2 pneumonitis on Day 36, and thoracic radiotherapy was terminated at 50 Gy. Patient 13 developed Grade 3 infection, and thoracic radiotherapy was completed after resolving this toxicity. Also, late Grade 3 pneumothorax occurred in this patient 6 weeks after completion of thoracic radiotherapy. Patient 14 had Grade 3 febrile neutropenia on Day 39 and Grade 2 pneumonitis on Day 42, and therefore thoracic radiotherapy was terminated at 56 Gy. Patient 15 developed severe pneumonitis 2 months after completion of chemoradiation and died on Day 116 despite steroid-pulse therapy. Patient 16 had Grade 3 esophagitis on Day 30 and thoracic radiotherapy was interrupted. After resolving this toxicity, thoracic radiotherapy was completed, but chemotherapy was not restarted.

Among 10 patients at this dose level, 5 patients developed DLTs and 3 patients developed Grade 2 or severe pneumonitis or other severe toxicities, including 1 treatment-related death; therefore, this dose level was also judged to be toxic. Treatment delivery is summarized in Table 2. Overall toxicities are summarized in Table 3 and DLTs and symptomatic pneumonitis in Table 4.

Table 5. First site of disease progression

	Dose level 1 (n = 10)	Dose level 2 (n = 6)
Local (in-field)	0	0
Distant	4	2
Local and distant	2	2

Eight and 4 patients at Dose Level 1 and 2, respectively, were assessable for response to treatment. Four patients were unable to be assessed for response because of treatment-related toxicities. A partial response was observed in 6 patients at Dose Level 1 and in 1 patient at Dose Level 2. At the time of analysis, 10 patients have been documented to have experienced disease progression. The first site of disease progression or relapse is listed in Table 5. Median overall survival was 23.8 months (95% confidence interval [95% CI], 11.5–36.0 months), and progression-free survival was 10.2 months (95% CI, 8.9–11.5 months) (Fig. 1).

DISCUSSION

This small series demonstrates an unacceptably high rate of severe pneumonitis in elderly unresectable NSCLC patients treated with vinorelbine concurrent with thoracic radiotherapy.Although single-agent vinorelbine for elderly patients with advanced NSCLC was reported to be feasible and effective, vinorelbine and concurrent thoracic radiotherapy were judged to be too toxic. We have sought to determine why this regimen was so much more toxic than expected. There are several possible explanations. The first is the radiosensitizing effect of vinorelbine not only for tumor cells but also for normal tissue. We set two vinorelbine levels, but

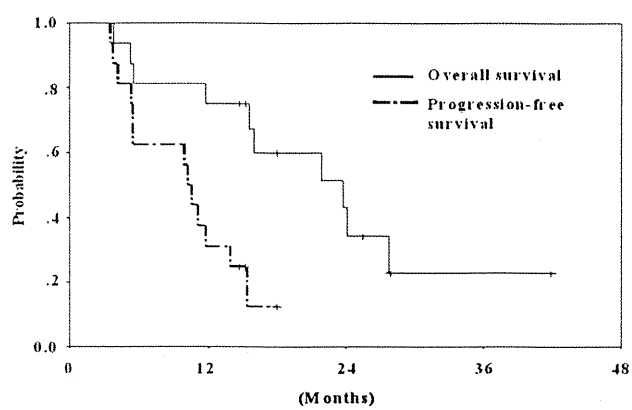

Fig. 1. Overall survival and progression-free survival of all 16 patients in the trial. Tick marks denote the censored observations.

Grade 2 or severe pneumonitis occurred at both. Sekine *et al.* (10) reported that thoracic radiotherapy concurrent with cisplatin and vinorelbine was feasible for unresectable NSCLC patients <75 years old. The recommended dose of vinorelbine is 20 mg/m^2 on Days 1 and 8 every 4 weeks.

In this study, although single-agent vinorelbine was adopted, Level 1 was 20 mg/m^2 on Days 1 and 8 every 3 weeks. There also have been a number of publications regarding the use of vinorelbine concurrently with radiotherapy in the setting of unresectable NSCLC (9–13). In these studies, vinorelbine dose intensity during thoracic radiotherapy was relatively lower than ours, which may have enhanced the normal tissue toxicities of radiotherapy in the present study. On the other hand, hematologic toxicities of this study were feasible and comparable to those of the single-agent vinorelbine arm in reported studies (6, 7, 16).

We also tried to evaluate radiotherapy planning. The ratio of normal lung volume irradiated at >20 Gy (V20) was reported to correlate with severe pneumonitis (17). The investigators in that study reported four cases of fatal pneumonitis; all of those cases occurred in patients with a V20>35%, and all high-grade pneumonitis occurred in patients with a V20 of >32%. Unfortunately, a dose–volume histogram was not available for all patients, but for 6 of 7 patients with Grade ≥2 pneumonitis were available. V20 in these patients was <32% (V20 <25% in 4 patients and 25% ≤V20 <32% in 2 patients). Fatal pneumonitis occurred in a patient with a V20 of 26%. Mean lung dose (MLD) was also evaluated. The range was from 9.3 to 16.8 Gy for these cases, and 13.2 Gy in the fatal pneumonitis case. It is reported that MLD of >18 Gy reportedly correlated with pneumonitis (18); however, the MLDs in the patients reported above were <18 Gy. Therefore, we consider that radiotherapy planning was not the major reason for the high rate of Grade ≥2 pneumonitis.

There are some other probable explanations for increasing toxicities. In elderly individuals, the amount of body fat is often increased and the intracellular water is decreased, resulting in increased distribution and prolonged half-life of lipophilic drugs, such as vinorelbine, which may enhance the radiosensitizing effect when given concurrently with thoracic radiotherapy. In the tested population, however, body mass index (19), in which the cut-off point for overweight and obesity were 25 kg/m^2 and 30 kg/m^2, respectively, ranged from 18 to 27, and only 2 patients were classified as overweight and none as obese. Tobacco consumption during the follow-up also may have affected the incidence of pneumonitis. In the tested population, all except 1 patient were current or past smokers; however, none had reported smoked during the follow-up period. Therefore, these factors do not have directly enhanced toxicities; however, there might be other factors such as mental status and emotional condition, nutritional status, polypharmacy, and the presence of geriatric syndromes that may limit the safety of concurrent chemoradiation for elderly patients. Socinski *et al.* (20) reported that age was not predictive for survival and that elderly patients derive benefits from chemoradiation similar to those of younger patients, whereas others (21, 22) reported that elderly patients did not benefit from increased therapeutic intensity. Ohe *et al.* (23) also reported that age was a significant risk factor for treatment-related death due to radiation pneumonitis for patients treated by thoracic radiotherapy. A Phase III trial of the Japan Clinical Oncology Group (JCOG9812) reported a high incidence of treatment-related death mainly due to pneumonitis in the chemo-radiation arm when using daily carboplatin concurrently with thoracic radiotherapy for the same population as ours (24). From these findings, elderly patients should be treated carefully, especially in regard to chemo-radiation therapy.

Although survival in our study must be assessed with caution because of the small number of cases and the brevity of the follow-up period, the overall survival is promising despite the treatment-related toxicities. However, even if an intensive treatment may prolong survival, too toxic a treatment is unacceptable for elderly patients because their quality of life is often more important than risking radical treatment. Several studies also reported that a reduced dose of vinorelbine and concurrent thoracic radiotherapy is feasible and promising (13). Therefore, the time has come to find both an active and less toxic dose and an appropriate schedule for this agent in elderly patients.

In conclusion, concurrent vinorelbine and thoracic radiotherapy resulted in a high incidence of severe pneumonitis when the standard dose of this agent was used for elderly patients. We therefore recommend caution in the use of this regimen and schedule for elderly patients.

REFERENCES

1. Kaneko S, Ishikawa KB, Yoshimi I, *et al.* Projection of lung cancer mortality in Japan. *Cancer Sci* 2003;94:919–923.
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer; a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J* 1995;311:899–909.
3. Furuse K, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17: 2692–2699.
4. Hanna N, Neubauer M, Yiannoutsos C, *et al.* Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: The Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* 2008;26:5755–5760.
5. Movsas B, Scott C, Sause W, *et al.* The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): A quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. *Int J Radiat Oncol Biol Phys* 1999;45:1143–1149.
6. Gridelli C. The ELVIS trial: A phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small-cell lung cancer. *Oncologist* 2001;6:4–7.

7. Gridelli C, Perrone F, Gallo C, *et al.* Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 2003;95:362–372.
8. Fukuoka K, Arioka H, Iwamoto Y, *et al.* Mechanism of radiosensitization induced by vinorelbine in human non-small-cell lung cancer cells. *Lung Cancer* 2001;34:451–460.
9. Gridelli C, Guida C, Barletta E, *et al.* Thoracic radiotherapy and daily vinorelbine as radiosensitizer in locally advanced non small cell lung cancer: A phase I study. *Lung Cancer* 2000;29:131–137.
10. Sekine I, Noda K, Oshita F, *et al.* Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95: 691–695.
11. Kobayashi M, Matsui K, Hirashima T, *et al.* Phase I study of weekly cisplatin, vinorelbine, and concurrent thoracic radiation therapy in patients with locally advanced non-small-cell lung cancer. *Int J Clin Oncol* 2006;11:314–319.
12. Vokes EE, Haraf DJ, Masters GA, *et al.* Vinorelbine (navelbine), cisplatin, and concomitant radiation therapy for advanced malignancies of the chest: A phase I study. *Semin Oncol* 1996; 23(Suppl):48–52.
13. Vokes EE, Herndon JE II, Crawford J, *et al.* Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B study 9431. *J Clin Oncol* 2002;20:4191–4198.
14. Japan Clinical Oncology Group, Japan Society of Clinical Oncology. Japanese translation of Common Terminology Criteria for Adverse Events (CTCAE), and instructions and guidelines. *Int J Clin Oncol* 2004;9(Suppl 3):1–82.
15. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
16. Kudoh S, Takeda K, Nakagawa K, *et al.* Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). *J Clin Oncol* 2006;24:3657–3663.
17. Graham MV, Purdy JA, Emami B, *et al.* Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999;45:323–329.
18. Barriger RB, Fakiris AJ, Hanna N, *et al.* Dose-volume analysis of radiation pneumonitis in non-small-cell lung cancer patients treated with concurrent cisplatinum and etoposide with or without consolidation docetaxel. *Int J Radiat Oncol Biol Phys* 2010;78:1381–1386.
19. World Health Organization. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363: 157–163.
20. Socinski MA, Zhang C, Herndon JE II, *et al.* Combined modality trials of the cancer and leukemia group B in stage III non-small-cell lung cancer: Analysis of factors influencing survival and toxicity. *Ann Oncol* 2004;15:1033–1041.
21. Langer C, Scott C, Byhardt R, *et al.* Effect of advanced age on outcome in radiation therapy oncology group studies of locally advanced NSCLC (LA-NSCLC). *Lung Cancer* 2000;29:104 [abstract].
22. Movsas B, Scott C, Sause W, *et al.* The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): A quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. *Int J Radiat Oncol Biol Phys* 1999;45:1143–1149.
23. Ohe Y, Yamamoto S, Suzuki K, *et al.* Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. *Eur J Cancer* 2001;37:54–63.
24. Atagi S, Kawahara M, Tamura T, *et al.* Standard thoracic radiotherapy with or without concurrent daily low-dose carboplatin in elderly patients with locally advanced non-small cell lung cancer: A phase III trial of the Japan Clinical Oncology Group (JCOG9812). *Jpn J Clin Oncol* 2005;35: 195–201.

Correlation Between ^{18}F-FDG Uptake on PET and Molecular Biology in Metastatic Pulmonary Tumors

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^{18}F-FDG PET can help in predicting therapeutic response and outcome in patients with metastatic pulmonary tumors. However, no satisfactory biologic explanation exists for this phenomenon. The aim of this study was to investigate the underlying biologic mechanisms of ^{18}F-FDG uptake in metastatic pulmonary tumors. **Methods:** One hundred forty-six patients with metastatic pulmonary tumors who underwent ^{18}F-FDG PET before treatment were included in this study. Tumor sections were stained by immunohistochemistry for glucose transporter 1 (Glut1), glucose transporter 3 (Glut3), hexokinase I, hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), and microvessel density determined by CD34. ^{18}F-FDG uptake and the expression of these biomarkers were correlated in primary lung cancer and benign pulmonary lesions. **Results:** ^{18}F-FDG uptake in metastatic pulmonary tumors correlated significantly with the expression of Glut1 ($\gamma = 0.4579$, $P < 0.0001$), HIF-1α ($\gamma = 0.3654$, $P < 0.0001$), hexokinase I ($\gamma = 0.3921$, $P < 0.0001$), VEGF ($\gamma = 0.5528$, $P < 0.0001$), and CD34 ($\gamma = 0.2342$, $P = 0.0044$). ^{18}F-FDG uptake in metastatic pulmonary tumors was significantly lower than in primary lung cancer but higher than in benign pulmonary lesions. High uptake of ^{18}F-FDG was significantly associated with poor outcome after pulmonary metastasectomy. In patients with metastatic pulmonary tumors, ^{18}F-FDG uptake and the expression of Glut1, HIF-1α, and VEGF were significantly higher in adenocarcinoma and squamous cell carcinoma than in sarcoma. ^{18}F-FDG uptake was significantly correlated with tumor size ($P < 0.0001$), but there was no significant relationship between tumor size and the expression of these biomarkers. **Conclusion:** The amount of ^{18}F-FDG uptake in metastatic pulmonary tumors is determined by the presence of glucose metabolism (Glut1), phosphorylation of glucose (hexokinase I), hypoxia (HIF-1α), and angiogenesis (VEGF and microvessel density).

Key Words: ^{18}F-FDG PET; pulmonary metastases; Glut1; hypoxia; angiogenesis

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The lungs are one of the major metastatic sites of neoplasms arising from other organs. If the radiologic findings are typical of pulmonary metastasis, clinicians usually diagnose it using CT of the chest. However, it is sometimes difficult to differentiate metastatic pulmonary nodules from primary lung cancer or benign lesions. In such a situation, ^{18}F-FDG PET may be useful for differentiating malignant tumors from benign lesions (*1,2*). However, ^{18}F-FDG PET is not useful in differentiating primary lung cancer from a solitary pulmonary metastasis. Therefore, resection of pulmonary metastasis has become an integral part of diagnosis and treatment if the primary malignancies outside the thorax are controlled. Recently, 1 report suggested that ^{18}F-FDG PET has a low sensitivity in the evaluation of metastatic pulmonary nodules when pulmonary metastasectomy is being considered (*3*). However, metastatic pulmonary nodules are a heterogeneous group of tumors, including such histologic types as squamous cell carcinoma (SQC), adenocarcinoma, and sarcoma. Because ^{18}F-FDG uptake is directly associated with glucose metabolism (*4*), the sensitivity of ^{18}F-FDG PET differs among the various histologic types of the primary malignancies. Little is known about the relationship between ^{18}F-FDG uptake and metastatic pulmonary tumors in patients receiving pulmonary metastasectomy.

Determination of malignant lesions with ^{18}F-FDG PET is based on glucose metabolism (*3–5*). The overexpression of glucose transporter 1 (Glut1) has been shown to be closely related to ^{18}F-FDG uptake in human cancer (*3–5*). Glut1 is thought to be a possible intrinsic marker of hypoxia, and the expression of Glut1 has been found to be regulated by hypoxia in a manner dependent on hypoxia-inducible factor-1α (HIF-1α) (*3–5*). Previous studies suggest that hypoxic conditions correspond to a higher ^{18}F-FDG uptake (*6–8*). In addition, several researchers described the relationship between ^{18}F-FDG uptake and the expression of vascular endothelial growth factor (VEGF) or microvessel density (MVD) (*9–11*). HIF-1α is considered to support tumor growth by the induction of angiogenesis via the expression of VEGF and by high and anaerobic metabolic

mechanisms (*12*). Because many factors can influence the extent of ^{18}F-FDG uptake, the underlying mechanisms for ^{18}F-FDG accumulation are still a matter of debate in various human neoplasms. However, there is still no relevant explanation of mechanisms for ^{18}F-FDG uptake in metastatic pulmonary tumor secondary to primary malignancies outside the thorax. Defining a correlation between these biomarkers and ^{18}F-FDG uptake may lead to a better understanding and interpretation of ^{18}F-FDG PET scanning in metastatic pulmonary tumors. On the basis of this background, we conducted ^{18}F-FDG PET studies and immunohistochemical analyses in patients with metastatic pulmonary tumors. We also evaluated the biologic correlation of ^{18}F-FDG PET in patients with primary lung cancer and benign pulmonary lesions as a solitary-pulmonary-nodule control group.

MATERIALS AND METHODS

Patients

We analyzed 169 consecutive patients who underwent ^{18}F-FDG PET and lung resection for pulmonary metastasis from extrathoracic malignancies at Shizuoka Cancer Center between April 2003 and May 2009. Patients who underwent PET before pulmonary metastasectomy were included in the study, whereas patients who had other malignancies or received induction chemotherapy or radiation before pulmonary metastasectomy were excluded. Six patients who received induction chemotherapy or radiation therapy were excluded. The specimens of 7 patients were not available. Ten patients were excluded from analysis because they did not undergo ^{18}F-FDG PET within 4 wk before their pulmonary resection was performed. Thus, 146 patients were analyzed in the study. All patients were imaged using ^{18}F-FDG PET.

We evaluated the biologic correlation of ^{18}F-FDG PET in patients with non–small cell lung cancer (NSCLC), as compared with metastatic pulmonary tumors, as an other-pulmonary-malignancy test group. NSCLC patients were consecutively assigned to in the study between December 2002 and March 2004, and ^{18}F-FDG PET was performed as part of the preoperative work-up. These patients underwent surgical management, and the primary lesions were surgically resected. Patients with NSCLC of the adenocarcinoma or SQC type were included in this study. NSCLC patients without visible tracer uptake on ^{18}F-FDG PET were excluded from this study. Finally, 138 patients with NSCLC (93 with adenocarcinoma and 45 with SQC) were evaluated. These 138 patients had no metastatic pulmonary tumors that were due to primary malignancies outside the thorax.

We also compared the biologic correlation of ^{18}F-FDG uptake between a control group of patients with benign pulmonary lesions and the group with metastatic pulmonary tumors. This control group had pulmonary lesions positive for ^{18}F-FDG uptake that had been surgically resected. Between November 2002 and August 2008, 29 consecutive such patients were included in this study. The histology of the resected benign pulmonary lesion was as follows: 11 epitheloid granulomas, 4 cryptococcomas, 4 sarcoidoses, 6 cases of inflammatory change, and 4 other types.

None of the patients had insulin-dependent diabetes, and the serum glucose levels in all patients just before ^{18}F-FDG PET were less than 120 mg/dL. The study protocol was approved by the institutional review board.

^{18}F-FDG PET

Patients fasted for at least 4 h before ^{18}F-FDG PET examination. They received an intravenous injection of ^{18}F-FDG (200–250 MBq) and then rested for approximately 1 h before undergoing imaging (*4*). Images were acquired using an Advance NXi PET scanner and Discovery PET/CT scanner (GE Healthcare). Two-dimensional emission scanning was performed from the groin to the top of the skull. PET/CT images were independently reviewed by 2 experienced physicians. Acquired data were reconstructed by iterative ordered-subset expectation maximization. The tumor was first examined visually for ^{18}F-FDG accumulation, and then the peak standardized uptake value (SUV) of the entire tumor was determined. Maximal SUV (SUV_{max}) was defined as the peak SUV on 1 pixel with the highest counts within the region of interest. The region of interest, measuring 3 cm in diameter, was set at the mediastinum at the level of the aortic arch, and the mean SUV of the mediastinum was calculated. Finally, the T/M ratio, which is the ratio of the peak SUV of the tumor to the mean SUV of the mediastinum, was determined for each patient.

Immunohistochemical Staining

Immunohistochemical staining was performed according to the procedure described in a previous report (*4*). The following antibodies were used: a rabbit polyclonal antibody against Glut1 (AB15309 [Abcam], 1:400 dilution), rabbit polyclonal antibody against glucose transporter 3 (Glut3) (AB15311 [Abcam], 1:100 dilution), mouse monoclonal antibody against HIF-1α (NB100-123 [Novus Biologicals, Inc.], 1:50 dilution), rabbit monoclonal antibody against hexokinase I (Abcam, 1:200 dilution), monoclonal antibody against VEGF (Immuno-Biologic Laboratories Co., Ltd., 1:300 dilution), and mouse monoclonal antibody against CD34 (Nichirei, 1:800 dilution).

The expression of Glut1 and Glut3 was considered positive if distinct membrane staining was present. Five fields (×400) were analyzed to determine the frequency of the HIF-1α–stained nuclei and hexokinase I–stained cytoplasm. For Glut1, Glut3, HIF-1α, and hexokinase I, a semiquantitative scoring method was used (1, <10%; 2, 10%–25%; 3, 25%–50%; 4, 51%–75%; and 5, >75% of cells positive). The tumors in which stained tumor cells made up more than 25% of the tumor were graded as positive.

The expression of VEGF was quantitatively assessed according to the percentage of immunoreactive cells in 1,000 neoplastic cells. The number of CD34-positive vessels was counted in 4 selected hot spots in a ×400 field (field area, 0.26 mm^2). MVD was defined as the mean count of microvessels per 0.26-mm^2 field area. Sections were assessed using light microscopy in a masked fashion by at least 2 of the authors.

Statistical Analysis

Probability values of less than 0.05 indicated a statistically significant difference. The Fisher exact test was used to examine the association of 2 categoric variables. Correlations between different variables were analyzed using the nonparametric Spearman rank test. The Kaplan–Meier method was used to estimate survival as a function of time, and survival differences were analyzed by the log-rank test. A receiver-operating-characteristic analysis was performed for determining a cutoff value of ^{18}F-FDG uptake between malignant and benign lesions. Statistical analysis was performed using JMP 8 (SAS Institute Inc.) for Windows (Microsoft).