Table 6 Response stratified according to various characteristics in all cases

Characteristic	No. of Patients	Response				Response rate (%) (95% CI)
		CR	PR	NC	PD	
Total	27	2	14	9	2	59.3 (38.8–77.6)
Stage						
IV	7	0	4	3	0	57.1 (18.4–90.1)
Recurrent	20	2	10	6	2	60.0 (36.1–80.9)
Histology						
Squamous cell carcinoma	20	1	11	7	1	60.0 (36.1–80.9)
Nonsquamous cell carcinoma	7	1	3	2	1	57.1 (18.4–90.1)
Prior therapy						
No	12	1	7	4	0	66.7 (34.9–90.1)
Yes	15	1	7	5	2	53.3 (26.6–78.7)
Site						
Inside radiation field	5	0	2	2	1	40.0 (5.3–85.3)
Outside radiation field	22	2	12	7	1	63.6 (40.7–82.8)
Age (years)						
≤50	10	1	7	1	1	80.0 (44.4–97.5)
>50	17	1	7	8	1	47.1 (23.0–72.2)

non-small-cell lung cancer and could not find the MTD, while the RD of CPT-11 (days 1 and 8)/254-S was 60/100 mg m^{-2}. Their data are somewhat surprising, because a previous study set the RD for 254-S monotherapy at 100 mg m^{-2} (Ota *et al*, 1992). In Oshita's study, 90% of the patients (38 out of 42) had not received prior therapy and 64% (27 out of 42) of the patients were male. In our study and that of Machida, however, 74 and 58% of the patients had received prior therapy and all of the patients were female, so such differences may explain the different results, but further investigation is required.

In previous studies of combination chemotherapy with CPT-11 plus 254-S, CPT-11 was given on days 1 and 8, but we only gave CPT-11 on day 1 in this study for the following reasons: (1) The combination of 254-S and CPT-11 was reported to show marked synergy in SBC-3 and PC-14 lung cancer cell lines (Kanazawa *et al*, 2001), with the synergistic effect being dependent on the treatment schedule and being produced by concurrent exposure to 254-S and CPT-11. They analysed the mechanism of this synergistic effect and demonstrated that the inhibition of topoisomerase I by CPT-11 was enhanced 10-fold in the presence of 254-S. (2) At present, platinum compounds are thought of as key drugs for cervical cancer, so we focused more on the platinum compound in this study based on these findings.

In patients with advanced or recurrent cervical cancer, most active single agents achieve overall response rates of 15–35% (Thigpen *et al*, 1981; Bonomi *et al*, 1985; Takeuchi *et al*, 1991; McGuire *et al*, 1996; Verschraegen *et al*, 1997; Ivrin *et al*, 1998; Morris *et al*, 1998).

Several combination chemotherapy regimens that contain cisplatin have been tested in phase II studies, and objective responses have been documented in 30–70% of the patients, while the median overall survival time ranged between 7 and 12 months (Buxton *et al*, 1989; Murad *et al*, 1994; Long *et al*, 1995; Papadimitriou *et al*, 1997, 1999; Rose *et al*, 1999). Although it is difficult to directly compare the relative merits of the combined regimens with the single agents, combination chemotherapy seems to be superior to single-agent therapy based on these phase II studies. A randomised study performed by the GOG in 438 assessable patients indicated that the combination of cisplatin and ifosfamide achieved a higher response rate and a longer progression-free survival time compared with cisplatin alone. However, the combination was more toxic and there was no difference of overall survival (Omura *et al*, 1997), suggesting the need to develop new combinations for advanced or recurrent cervical cancer. In this study, the overall response rate was 59%, while among the 12 responders with recurrent disease, the median time to progression and median survival time were 161 days (range: 61–711 days) and 415 days (range: 74–801 days), respectively. Thus, the regimen seems to be promising for treating advanced or recurrent cervical cancer.

Brader *et al* (1998) reported that the site of recurrence (inside the radiation field or outside it) and the age of the patient could predict the response to chemotherapy for cervical cancer. In addition, adenocarcinoma is thought to be more resistant to chemotherapy compared with squamous cell carcinoma. In the present study, both squamous cell carcinoma and adenocarcinoma were sensitive to the combination of CPT-11 plus 254-S. However, this regimen tend to be more effective for disease recurring outside the radiation field than for recurrence inside the radiation field (RR; 64 *vs* 40%). In addition, this regimen tend to be more effective for young patients.

In conclusion, the RD of CPT-11/254-S with rhG-CSF was 50/80 mg m^{-2}, and this regimen seems to be promising for treating advanced or recurrent cervical cancer.

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Original contribution

Gemcitabine/Carboplatin in a Modified 21-Day Administration Schedule for Advanced-Stage Non–Small-Cell Lung Cancer

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Abstract

PURPOSE: Gemcitabine/carboplatin is active for advanced-stage non–small-cell lung cancer. Although it has a better toxicity profile than gemcitabine/cisplatin, severe thrombocytopenia can be a problem. We conducted a phase II study of gemcitabine/carboplatin on a 21-day schedule with administration of carboplatin delayed until day 8, intending to decrease the severity of thrombocytopenia and evaluate the feasibility and efficacy of this schedule. PATIENTS AND METHODS: Thirty-one patients with stage IIIB or stage IV non–small-cell lung cancer received gemcitabine 1000 mg/m^2 on days 1 and 8 and carboplatin at an area under the curve of 5 mg × minute/mL on day 8, every 21 days. RESULTS: The response rate was 22.6%, including 1 complete response. The median time to progression was 161 days, and the median survival was 454 days. Grade 3/4 thrombocytopenia, according to the National Cancer Institute Common Toxicity Criteria, version 3.0, was observed in 2 patients (6.5%) in the first 2 cycles. Nonhematologic toxicity included rash, depression, fever, nausea/vomiting and increased hepatic transaminase. The median courses of delivery were 3, and 13 patients (42%) received the first 3 courses without treatment delay. Dose intensity for each drug was 638 mg/m^2 per week for gemcitabine and 1.56 mg × minute/mL per week for carboplatin area under the curve, respectively. CONCLUSION: This study suggests that gemcitabine/carboplatin with a day-8 administration of carboplatin in a 21-day schedule reduces the severity of thrombocytopenia without having a detrimental effect on efficacy.

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Key words: Dose intensity, Feasibility, Phase II studies, Thrombocytopenia

Introduction

Non–small-cell lung cancer (NSCLC) constitutes 75%-80% of lung cancer cases and currently represents a leading cause of cancer-related death throughout the world.[1] Significant proportions of the patients present with locally advanced or metastatic disease at the time of diagnosis.[2] Although a recent overview suggested that platinum agent–based chemotherapy improves survival and quality of life,[3] the long-term prognosis of these patients is still generally poor. In the past 2 decades, several new chemotherapeutic agents have been developed and have proven to be active in advanced-stage NSCLC. Gemcitabine, a pyrimidine antimetabolite, is one of the most promising among these agents, showing definite efficacy and mild toxicity profiles. Initial phase I studies using a schedule of weekly administrations of 3 weeks for every 4 weeks established 790 mg/m^2 weekly as the maximum tolerated dose. Dose-limiting toxicity was myelosuppression, with thrombocytopenia more significant than granulocytopenia.[4] Later phase I/II studies have established 1250 mg/m^2 weekly as an optimal tolerated dose.[5-7] Several phase II studies of single-agent gemcitabine in advanced-stage NSCLC have demonstrated response rates of 20%-26% and a median survival of 7-9.4 months.[8-13] In these studies, 800-1250 mg/m^2 gemcitabine was administered weekly for 3 weeks every 4 weeks. Toxicities reported in these studies were myelosuppression, such as granulocytopenia and thrombocytopenia, transient increase of hepatic transaminases, rash, flu-like symptoms, and lethargy.

The combination of gemcitabine and a platinum compound has demonstrated a synergistic effect in preclinical settings, and a number of phase II/III studies of gemcitabine/cisplatin have been performed.[14-22] This combination chemotherapy has proved to be very promising, showing

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an objective response rate (ORR) of 28%-54% and a median survival of 8.4-15.4 months. Gemcitabine/cisplatin is now one of the standard chemotherapy combinations for advanced-stage NSCLC. However, the toxicity profile of cisplatin, such as nausea/vomiting, nephrotoxicity, and neurotoxicity, can be troublesome for patients with advanced-stage NSCLC, who generally have poor prognosis. Moreover, cisplatin is often intolerable for certain patients, especially the elderly and/or those with concomitant severe diseases. Carboplatin is a cisplatin analogue, and its nonhematologic toxicity is milder compared with cisplatin. Carboplatin is also expected to exert a synergistic effect with gemcitabine. Several phase II studies of gemcitabine/carboplatin have been reported. The early studies adopted a schedule of weekly administration of gemcitabine for 3 weeks (day 1, 8, and 15 administrations) and day-1 administration of carboplatin every 4 weeks.[23-29] However, those studies reported high incidences of thrombocytopenia, prompting the investigation of other schedules that are less myelosuppressive. Iaffaiolli et al recommended a 28-day schedule that decreased myelotoxicity around day 15 by administrating carboplatin on day 8 and eliminating the administration of gemcitabine on day 15.[30] Edelman et al recommended a 21-day schedule that decreased myelotoxicity around day 15 by simply eliminating the administration of gemcitabine on day 15.[31] Several large phase II studies have been performed using these schedules. Among them, Mott et al reported a phase II study with a 28-day schedule described by Iaffaiolli et al, with an ORR of 10% and a median survival of 8.3 months.[32] On the other hand, Yamamoto et al reported the results of a comparative phase II study in which a 21-day schedule described by Edelman et al was compared with gemcitabine/vinorelbine as a control arm.[33] The ORR of gemcitabine/carboplatin was 20%, and the median survival of 432 days was favorable. However, a high incidence of dose reduction as a result of myelosuppression and early withdrawal from the study were reported. These studies suggest that the schedule for gemcitabine/carboplatin still needs improvement. In the present article, we report another 21-day schedule, with the intent to be more dose intense than Mott et al and less myelosuppresive than Yamamoto et al.

Patients and Methods

Eligibility Criteria

Eligibility criteria of patients were as follows: age 20-80 years, a histologic or cytologic diagnosis of clinical stage IIIB NSCLC with malignant pleural effusion or clinical stage IV NSCLC, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2. Patients were required to have adequate bone marrow reserve (leukocyte count > 4000/μL, platelet count > 100,000/μL, and hemoglobin > 10 g/dL), normal hepatic function (serum bilirubin < 1.5 mg/dL, transaminases < 2 times the upper limit of normal), normal renal function (serum creatinine < 1.2 mg/dL), and a life expectancy of > 3 months. Patients who did not have measurable disease based on Response Evaluation Criteria in Solid Tumors[34] were excluded from the study. Neither previous chemotherapy nor thoracic irradiation was allowed. Patients were excluded from the study when they met one of the following conditions: active uncontrolled infection, unstable concomitant disease (ischemic heart disease, hypertension, or diabetes mellitus), active concomitant malignant disease, pregnancy, or breastfeeding. Written informed consent was obtained from all patients.

Study Design

This was a single-arm phase II study. Because the response rate of gemcitabine/carboplatin has been reported by a variety of authors, we determined the primary endpoint of our study as the rate of treatment completion without treatment delay. It has been reported that the median courses of delivery of platinum-doublet chemotherapy was approximately three[35] and that there was no statistical significance in survival of patients between 3 and 6 courses of platinum agent–containing chemotherapy.[36] Therefore, we analyzed drug delivery in the first 3 courses to evaluate the feasibility of the schedule and defined the treatment completion rate to be the percentage of patients who received the first 3 courses with no delay from the intended schedule. The expected and threshold value of the treatment completion rates were 90% and 70%, respectively. The number of patients required was determined with an α risk of 0.05 and a β risk of 0.2. Simon's optimal design was applied to recruit the patients[37]: if completion of treatment was observed in < 5 patients among the first 6 patients, the study was to be terminated; if it was observed in ≥ 5 patients, recruitment of as many as 27 patients was allowed. This schedule was judged to be feasible when, in an analysis of 27 patients, treatment completion was observed in > 22 patients. The secondary endpoints included the evaluation of response rate, toxicities, median time to progression (TTP), and overall survival. This study was approved by the Institutional Review Board of Osaka Medical Center for Cancer and Cardiovascular Diseases.

Treatment Plan

Patients received carboplatin at an area under the curve (AUC) of 5 mg × minute/mL, calculated using the Calvert formula[38] with creatinine clearance evaluation by the Cockcroft formula.[39] Carboplatin was administrated in a 60-minute infusion on day 8 of a 21-day cycle. Gemcitabine was administrated at 1000 mg/m^2 in a 30-minute infusion on days 1 and 8. The planned dose intensity for each drug was 667 mg/m^2 per week for gemcitabine and 1.67 mg × minute/mL every week for carboplatin AUC. Four cycles of treatment were intended. On day 1 and day 8 of each cycle, complete blood count was evaluated. Drug administration was delayed until recovery in cases with leukocyte count < 3000/μL or platelet count < 100,000/μL on day 8.

The hematologic criteria to start the next cycles were loosened to increase dose intensity (leukocyte count > 2500/μL

Table 1 Patient Characteristics (N = 31)

Characteristic	Number of Patients
Median Age, Years (Range)	63 (42-76)
Sex	
Male	12
Female	19
Stage	
IIIB	8
IV	23
Histology	
Adenocarcinoma	25
Squamous cell carcinoma	6
ECOG PS	
0	22
1	9

and platelet count > 75,000/μL). The start of the new cycles was postponed until blood count met these criteria. Doses of gemcitabine were adjusted according to leukocyte, neutrophil, and platelet counts. If grade 4 leukopenia or neutropenia continued > 3 days despite the use of granulocyte colony-stimulating factor or if platelet count decreased to < 25,000/μL, the gemcitabine dose was reduced by 200 mg/m^2 intervals until 600 mg/m^2. Patients were withdrawn from the study in cases of disease progression, development of grade > 3 nonhematologic toxicities, unacceptable treatment delay as a result of hematologic toxicities, or necessity of gemcitabine dose reduction to < 600 mg/m^2. After withdrawal from the study, subsequent treatment was to be decided by the investigator.

Evaluation

Response was evaluated by chest and abdominal computed tomography (CT) scans after the second and fourth cycles of chemotherapy according to Response Evaluation Criteria in Solid Tumors. Brain magnetic resonance imaging, chest CT scan, and abdominal CT scan were performed at any time if assessment for the disease progression was necessary. Confirmation was necessary to determine partial and complete response. During the study, all enrolled patients were evaluated weekly by physical examination, complete blood count, and blood chemistries. Toxic effects were graded according to National Cancer Institute Common Toxicity Criteria, version 3.0.

Statistical Analysis

Time to progression was calculated from the date of enrollment to the date of progression using the Kaplan-Meier method.[40] Overall survival was calculated from the date of enrollment until the date of death or last known contact using the Kaplan-Meier method. Statistical analysis in the study was carried out using the SPSS program.

Table 2 Hematologic Toxicities

Adverse Event	Grade 3	Grade 4	N (%)
Leukopenia	10	0	10 (32.2)
Neutropenia	16	5	21 (67.7)
Anemia	3	0	3 (9.7)

Results

From June 2003 to April 2005, 31 eligible patients were enrolled in the study. There were 12 men and 19 women; 6 patients with squamous cell carcinoma and 25 with adenocarcinoma; 8 patients with clinical stage IIIB and 23 with clinical stage IV; 22 patients with an ECOG PS of 0 and 9 with a PS of 1. Sixteen patients had a smoking history. Patient characteristics are summarized in Table 1. Tumor response was assessable in all 31 patients. One complete response and 6 partial responses were observed, resulting in a response rate of 22.6%. Median TTP was 161 days (95% confidence interval, 109-213 days). At the time of analysis, when the median follow-up time was 356 days (range, 40-946 days), 12 patients were alive, 16 patients were dead, and 3 patients were lost to follow-up. Median survival time was 454 days (95% confidence interval, 230-678 days).

Toxicity profiles are summarized in Tables 2, 3, and 4. Table 2 shows hematologic toxicities except thrombocytopenia in the first 2 cycles. Neutropenia was frequently observed, with grade 3/4 neutropenia occurring in 51.6% (16 of 31 patients) and 16.1% (5 of 31 patients) of the patients, respectively. However, febrile neutropenia was not observed. Grade 3 anemia was observed in 9.7% of patients (3 of 31 patients), and grade 4 anemia was not observed. The incidence of red blood cell and platelet transfusions was 3.2% (1 of 31 patients) and 3.2% (1 of 31 patients), respectively. Because the grading of thrombocytopenia is substantially different among versions of the National Cancer Institute Common Toxicity Criteria, we show detailed results of platelet numbers in Table 3. Thrombocytopenia was relatively mild; grade 3/4 thrombocytopenia occurred in 3.2% (1 of 31 patients) and 3.2% (1 of 31 patients) of patients in the first 2 cycles, without serious hemorrhagic events. The lowest platelet count was 15,000/μL and was observed in the first cycle in a 74-year-old man. Grade 2/3 nausea/vomiting occurred in 3.2% (1 of 31 patients) and 3.2% (1 of 31 patients) of patients, respectively, grade 2 and 3 rash in 6.5% (2 of 31 patients) and 12.9% (4 of 31 patients), grade 3 depression in 3.2% (1 of 31 patients), grade 1 fever (in the absence of neutropenia) in 3.2% (1 of 31 of patients), and grade 1 hepatic transaminase increase in 9.7% (3 of 31 patients). A total of 94 cycles with a median of 3 cycles for each patient were administered. Treatment was delayed in 42.6% of cycles and required dose reduction in 6.4% of cycles. The median number of days per cycle was 24 days (22, 29, and 26 days for the first, second, and third cycles, respectively). The dose intensity was 638 mg/m^2 per week for gemcitabine and 1.56 mg × minute/mL per week for carboplatin AUC.

Table 3 Thrombocytopenia Incidence

Thrombocytopenia	N	Overall	1/2 Cycles	≥3 Cycles
Grade 3/4	31	2/3 (16.2%)	1/1 (6.5%)	1/2 (9.7%)

Nadir platelet counts in 5 cases with grade > 3 thrombocytopenia (× 10^4) were 1.5, 2, 2.5, 3.9, and 4.9.

Table 4 Nonhematologic Toxicities

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	2	1	1	0
Rash	0	2	4	0
Depression	0	0	1	0
Fever (Absence of Neutropenia)	1	0	0	0
Transaminase	3	0	0	0

Among the first 6 patients, 5 had ≥ 3 treatment cycles without treatment delay (4, 3, 2, 8, 4, and 4 cycles for the first, second, third, fourth, fifth, and sixth patients, respectively). Final analysis revealed that 21 of 31 patients received ≥ 3 treatment cycles, but 8 of these patients experienced treatment delay in the first 3 cycles. The treatment completion rate was not sufficiently high at 42%. Ten patients were withdrawn from the study early; the reason for withdrawal was progressive disease for 2 patients, hematologic toxicity for 3 (all were neutropenic but did not have thrombocytopenia), and nonhematologic toxicity for 5 (grade 3 depression in 1 patient and grade 3 rash in 4 patients; 1 was caused by carboplatin, and the others were caused by gemcitabine).

Discussion

Third-generation chemotherapy, consisting of a platinum agent and a third-generation chemotherapeutic agent, including gemcitabine, is considered a standard treatment for advanced-stage NSCLC worldwide. Many studies were carried out to compare the toxicity and efficacy of each regimen of third-generation chemotherapy. According to the ECOG 1594 study, a significant difference in efficacy is difficult to demonstrate among the regimens.[41] In contrast, the profiles of toxicities were demonstrably different among the regimens.

Although platinum compounds, such as cisplatin and carboplatin, are still key drugs in chemotherapy for NSCLC, a recent metaanalysis suggested that treatment with regimens containing gemcitabine showed small but statistically significant improvement in patient survival.[42] With its mild toxicity and easiness in administration, gemcitabine is becoming another key drug in chemotherapy for NSCLC. In a Japanese phase III trial in which gemcitabine/vinorelbine/paclitaxel in combination with a platinum agent were compared with irinotecan/cisplatin, a Japanese standard for NSCLC, gemcitabine/cisplatin exerted the best result; however, the difference was not statistically significant.[35] Recent trials showed that the gemcitabine/carboplatin improved patient survival compared with gemcitabine alone and mitomycin/ifosfamide/cisplatin.[43,44] Taking these results together, gemcitabine/carboplatin is a reasonable combination and becoming widely used for NSCLC.

Early studies of gemcitabine/carboplatin used a 28-day schedule in which gemcitabine was administered on days 1, 8, and 15 and carboplatin was administered on day 1.[23-29] However, because of a high incidence of severe thrombocytopenia, 2 alternate schedules were proposed: one is a 21-day schedule treatment in which gemcitabine is administered on days 1 and 8 with carboplatin administered on day 1,[31] and the other is a 28-day schedule in which gemcitabine is administered on day 1 and 8 with carboplatin on day 8.[30] Obasaju et al conducted a randomized phase II study comparing these 2 schedules.[45] Although the study was not powered to show a statistically significant difference between these 2 regimens, the 21-day schedule seemed to be superior to the 28-day schedule in terms of efficacy. However, grade 3/4 thrombocytopenia was observed in 14% of cycles in the 21-day schedule, higher than that in the 28-day schedule. The 21-day schedule has been used in several other studies, in which thrombocytopenia was still the main problem, accompanied by bleeding episodes, although not frequently.[27,46,47] In the Japanese phase II study described previously, thrombocytopenia was again a major issue, resulting in a high incidence of dose reduction and early withdrawal from the study.[33] Nevertheless, good median survival time of the patients treated with gemcitabine/carboplatin (432 days) and low incidences of nonhematologic toxicities were impressive. Meanwhile, the 28-day schedule in which carboplatin was administered on day 8 appeared to be less myelotoxic than the 21-day schedule but has the problem of low dose intensity.

Our study was designed to evaluate the feasibility and efficacy of gemcitabine/carboplatin in a modified administration schedule. Gemcitabine/carboplatin were administered at 1000 mg/m^2 on days 1 and 8 and at AUC 5 on day 8 of each 21-day cycle, respectively. The main aim of this study was to decrease the severity of thrombocytopenia with minimal effect on dose intensity. The low incidence of grade 3/4 thrombocytopenia was notable, observed in only 2 of 31 patients in the first 2 cycles. This result suggested that the nadir of thrombocytopenia of gemcitabine and carboplatin occur around day 15, and that incidence of severe thrombocytopenia could be decreased even in a 21-day schedule by delaying administration of carboplatin until day 8. We were concerned whether this 3-weekly chemotherapy would become possible by adopting looser criteria (leukocyte count > 2500/μL and platelet count > 75,000/μL) to start new cycles. Other hematologic and nonhematologic toxicities were also mild, and altogether, the treatment was well tolerated. The incidence of stressful toxicities represented by nausea/vomiting, neurologic toxicities, and alopecia was relatively low in the gemcitabine/carboplatin combination.

The planned dose intensities and actual dose intensities were 667 mg/m^2 per week and 638 mg/m^2 per week (95.7% of planned dose intensity) for gemcitabine and 1.67 mg ×

minute/mL per week and 1.56 mg × minute/mL per week (93.4% of planned dose intensity) for carboplatin AUC, respectively. Dose intensity for each drug in the 28-day schedule described previously[30,32] was estimated to be 550 mg/m^2 per week for gemcitabine and 1.25 mg × minute/mL per week for carboplatin AUC, respectively. The median cycles of delivery were 3, which was comparable with those of platinum-doublet chemotherapy.[35] Therefore, our main purpose to decrease the incidence of thrombocytopenia and increase dose intensity was achieved, although there are still problems to be solved.

Drug administrations were frequently delayed, treatment time tended to be protracted, and the treatment completion rate we defined was 42%. Unfortunately, early withdrawal from the study was seen in 10 patients (32%). Among these patients, 3 experienced grade > 2 leukopenia (leukocyte count < 3000/μL) on day 8 of the first course, and the other 3 patients developed grade 3 rash after administration of day 1 gemcitabine. For these 6 patients, gemcitabine/carboplatin chemotherapy was considered inappropriate regardless of the schedule. This schedule, which delays carboplatin administration until day 8, would enable early exclusion of the patients who are inappropriate for this combination chemotherapy, avoiding severe hematologic and nonhematologic toxicities. Response rate, median TTP, and median survival time were favorable. However, this might be biased by the small number of patients and the high percentage of patients with good prognostic factors such as female sex and PS of 0 in this study.

Recently, prolonged administration of gemcitabine combined with carboplatin has been tested.[48,49] Because gemcitabine/carboplatin combination chemotherapy has become a widely used regimen, further improvement of this regimen is necessary.

Conclusion

The present study suggests that carboplatin administered on day 8 in a 21-day schedule of gemcitabine/carboplatin reduces severity of thrombocytopenia without having a detrimental effect on efficacy. However, further evaluation is still needed to estimate the efficacy and feasibility of this regimen. The ongoing randomized phase II study compares day-1 and day-8 administration of carboplatin in a 21-day schedule of gemcitabine/carboplatin. In clinical practice, this regimen will be one of the treatment options suitable for outpatients.

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Improved Diagnostic Efficacy by Rapid Cytology Test in Fluoroscopy-Guided Bronchoscopy

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Background: Fluoroscopy-guided bronchoscopy is a safe and routine method used to obtain a histologic or cytologic specimen of peripheral lung nodules, but it has low sensitivity in diagnosing malignant tumors. Although feedback from rapid cytology tests are expected to improve diagnostic rates, the value of the routine use of rapid cytology tests has not been established.

Materials and Methods: We prospectively studied 657 patients with suspected peripheral malignant lung lesions on chest computed tomography who underwent fluoroscopy-guided bronchoscopy between January 2002 and December 2004. Rapid on-site cytopathologic examinations (ROSE) were performed during bronchoscopic examinations. The additional approach to the lesions was performed immediately after conventional bronchoscopic examinations when ROSE was not considered diagnostic.

Results: There were 528 patients diagnosed as having malignant lesions. In 477 of these patients (90.3%), final malignant diagnosis was established by the initial bronchoscopy. Among these, 84 patients (15.9%) were diagnosed only with the additional feedback from ROSE. Of 240 peripheral lesions ≤2 cm, 174 were found to be malignant. Without ROSE, 110 (63.2%) of peripheral malignant lesions were diagnosed by bronchoscopy. The integration of ROSE enabled us to diagnose an additional 40 patients (23.0%) by bronchoscopy. ROSE improved diagnostic yield independent of the site and histology of the lesions and experience of the operators.

Conclusion: ROSE increased the diagnostic yield of bronchoscopy from 74.4% to 90.3% and therefore is an effective reinforcement in bronchoscopic diagnosis of peripheral pulmonary malignancies. The use of ROSE in routine bronchoscopy should be encouraged.

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Examinations used to diagnose pulmonary malignant lesions should be safe, accurate, and optimal for obtaining adequate information. A flexible fiberoptic bronchoscope has become prevalent in obtaining specimen from lung lesions. Although central visible tumors can be diagnosed at high sensitivity, it is reported that the diagnostic rate for peripheral lung lesions is low, from 62% to 86%, even in combination with various techniques.[1–4] Brush, curette, forceps, and aspiration needles have been investigated as tools to obtain diagnostic specimens. Other reports recommend rapid on-site cytopathologic examinations (ROSE) in transbronchial needle aspiration of lymph nodes.[5–7] However, ROSE has not been introduced for diagnosing peripheral lung lesions. Recently, the combination of ultra-fast Papanicolaou staining and multiplanar reconstruction images has been recommended to improve diagnostic accuracy and safety in fluoroscopy-guided transbronchial biopsy.[8] In this prospective study, we integrated ROSE into routine bronchoscopy and evaluated the benefit of bronchoscopy combined with ROSE.

BRONCHOSCOPY

In our hospital, we foremost recommend bronchoscopy with a flexible bronchoscope in the diagnosis of pulmonary nodules because of its safety. If the lesions are not bronchoscopically invisible, procedures to obtain diagnostic materials are performed under fluoroscopic guidance. Transcutaneous fine-needle biopsy (TCNB) is recommended for patients with a negative result of preceding bronchoscopy or with negligible risk of pneumothorax by percutaneous puncture, such as those with lesions invading the thoracic wall. Video-assisted thoracic surgery (VATS) is usually recommended for patients with negative results of bronchoscopy and/or TCNB or lesions unrecognizable under fluoroscopy. For pure GGO, we recommend computed tomographic (CT) follow-up, otherwise VATS.

In bronchoscopy, the specimen for cytology was obtained by curetting or brushing. The material was smeared on two glass slides: one was subjected to ROSE (ROSE sample) and the other to conventional Papanicolaou staining. During ROSE, forceps biopsy was performed to obtain the specimen for histology and cytology. When ROSE was not diagnostic, additional bronchoscopic examinations, such as transbronchial needle aspiration (TBNA), bronchial washing, or ultrathin bronchoscopy, were performed to obtain additional samples just after conventional bronchoscopy. For the analysis, we defined both the material subjected to Papanicolaou staining and the material obtained by biopsy as conventional

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samples. The material obtained by additional bronchoscopic examinations after ROSE was defined as additional samples.

CYTOLOGY AND HISTOLOGY EXAMINATION

We used rapid Shorr stain as a rapid cytology test, which we have recently developed by modifying the Shorr stain.[9] Rapid Shorr stain completes staining very fast (approximately 1 minute) and presents similar coloring to Papanicolaou staining; therefore, it is familiar to the cytoscreeners in our institute. The cytopathologist was able to provide a preliminary diagnosis within a few minutes. Papanicolaou staining was performed after bronchoscopic examination. Tissue specimens obtained by forceps biopsy were fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin. Additional specific staining was performed when necessary.

PATIENTS

We performed 1900 flexible bronchoscopic examinations between January 2001 and December 2004. Based on the results of chest radiograph and CT, 795 patients were thought to have central lesions and underwent bronchoscopy without fluoroscopy; 1105 patients underwent fluoroscopy-guided bronchoscopy. ROSE was not performed in the examinations to obtain samples for bacterial testing, for visible lesions, or to evaluate lesions diagnosed before, etc. ROSE was not used for the patients entered into another study performed during the same period in which ROSE was not integrated. Other patients' samples were not subjected to ROSE because only a single trial to obtain bronchoscopic material was possible because of patients' stress during bronchoscopy. Excluding these from the 1105 patients who underwent fluoroscopy-guided bronchoscopy, 657 patients received fluoroscopy-guided bronchoscopy with ROSE. ROSE was repeated when we thought it possible and necessary. Despite negative ROSE results, the lesions of very likely malignant or difficulty except for bronchoscopy, we tend to repeat ROSE. If a diagnosis could not be made via bronchoscopy, further work-up for the lesions included surgical procedures, TCNB, follow-up by bronchoscopy, chest radiograph and CT, and sputum investigations.

RESULTS

Bronchoscopic examinations with ROSE were performed under fluoroscopic guidance for 657 peripheral lung lesions. Patient characteristics are listed in Table 1. The final diagnosis of malignant and benign disease was determined in 528 and 117 lesions, respectively. The remaining 12 lesions were not diagnosed and subjected to careful follow-up. Malignant lesions consisted of adenocarcinoma (n = 328), squamous cell carcinoma (n = 87), small cell carcinoma (n = 32), carcinoid (n = 20), large call carcinoma (n = 7), lymphoma (n = 3), metastatic carcinoma (n = 22), and other malignancies (n = 29).

As shown in Table 2, 393 lesions were diagnosed as malignant by using conventional samples alone. ROSE definitively detected malignant cells in 357 malignant lesions but failed to detect atypical cells in 36 malignant lesions. The false-negative rate of ROSE was 9.2% compared with diagnosis based on conventional samples. In ROSE, a limited time period is permitted for screening and diagnosis. However, cancer cells were detected in only one sample with a negative ROSE result by subsequent re-diagnosis with sufficient time. There was no false-positive result in ROSE. However, final diagnosis was obtained with the additional samples in 84 of 135 malignant lesions that were not diagnosed with conventional samples alone. Therefore, the integration of ROSE into bronchoscopic examination improved the diagnostic sensitivity from 74.4% to 90.3% (Figure 1*A*). The improvement of sensitivity was statistically significant ($p < 0.05$) and enabled effective diagnosis for peripheral lung lesions.

TABLE 1. Patient characteristics

Sex	All patients	Patients with malignancy
Male	411	344
Female	246	184
Age (year)		
Range	25–89	27-87
Average	65.7	66.5
Chance of discovery		
Annual screening	250	183
Tests for other diseases	223	176
Subjective symptoms	163	151
Others	21	18
Smoking status		
Smoker	223	190
Ex-smoker	161	136
Non-smoker	210	156
Unknown	63	46

Additional samples for diagnosis were collected by brushing, curetting, forceps biopsy, TBNA, ultra-thin-bronchoscopy, and washing from the same or other bronchi. Sometimes, several methods were combined for obtaining a specimen. The methods to obtain additional specimens were determined based on the bronchoscopic access to the lesions and the condition of patients. We analyzed additional approaches contribute to the improvement of diagnostic accuracy (Table 3). Whereas brushing showed low diagnostic yield, curetting or forceps biopsy from the other branch, TBNA, and forceps biopsy with ultra-thin bronchoscope yielded more than a 65% positive rate in additional approaches. Washing was also useful for diagnosis in additional approaches, but malignant cells were usually detected by the other methods conducted at the same time.

Surprisingly, ROSE provided more benefit for the diagnosis of small-sized lesions (≤2 cm) (Figure 1*B*). With conventional samples, 110 of 174 small-sized malignant lesions (63.2%) were diagnosed by bronchoscopy. With the help of ROSE, 40 lesions (23.0%) were diagnosed only with an additional sample. Improvement of diagnostic rate for small lesions was significantly greater than that for larger lesions (23.0% versus 12.4%; $p < 0.05$). No significant improvement was observed among the other factors in exam-

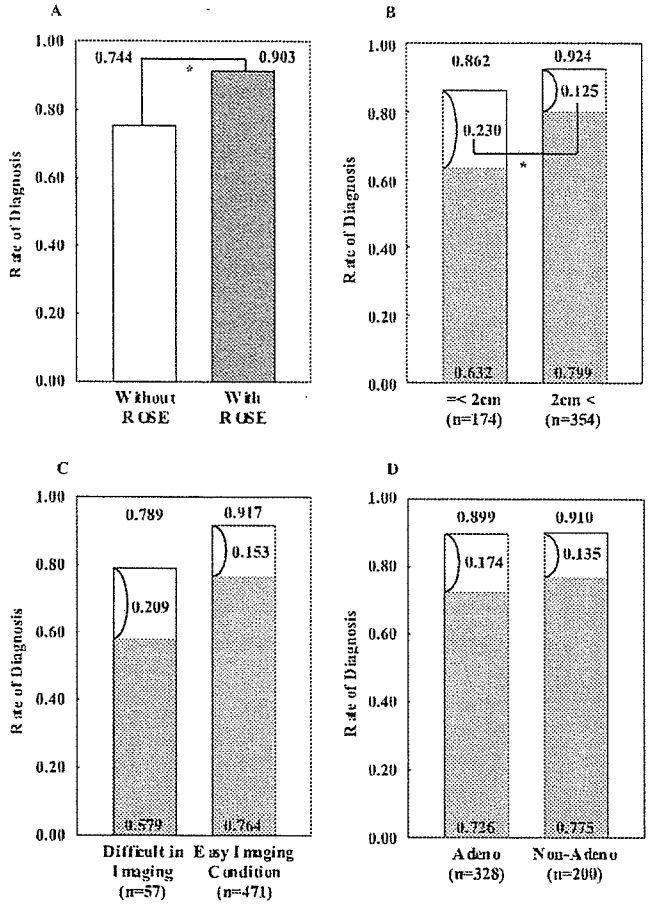

FIGURE 1. ROSE improved diagnostic yield and lesion features. *A*, ROSE improved diagnostic sensitivity. The *gray bar* shows the diagnostic sensitivity of fluoroscopy-guided bronchoscopy with ROSE; the *white bar* shows the diagnostic sensitivity of bronchoscopy without ROSE. The sensitivity is significantly different ($p < 0.05$). *B*, Tumor size and improvement of diagnostic sensitivity by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE. The improvement in small lesions was better than that in large lesions ($p < 0.05$). *C*, Imaging conditions of the lesions under fluoroscopy revealed diagnostic yield but little difference in improvement by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE. *D*, Histology type made little difference in diagnostic sensitivity and improvement by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE.

inations (Figure 1, *C* and *D*). Examination of poorly visible lesions in fluoroscopy had low sensitivity (n = 57, 78.9%) compared with that of clearly visible lesions (n = 471, 91.7%). The improvement by ROSE was slightly higher in examinations for poorly visible lesions (21.1% versus 15.3%), although the difference was not statistically significant. Little improvement by ROSE was shown between histology types of the lesions: adenocarcinoma 52.3%, squamous cell carcinoma 56.3%, small cell carcinoma 50%, and metastatic carcinoma 40.0% of ROSE-negative lesions. Our results also showed the difficulty in diagnosing lesions in the upper lobe and S6, especially in right lung with conventional samples. However, a comparable improvement of diagnostic yield was achieved with ROSE in most areas (from 40% to 60% of ROSE-negative lesions). We calculated the diagnostic yields with conventional samples and additional samples for each examiner to determine the effect of skill level of examiners on usefulness of ROSE. Although the skill level of the examiner tends to correlate to diagnostic yield with conventional samples, improved diagnosis by ROSE was observed similarly in almost all of the examiners (approximately 40% to 52% of ROSE-negative cases).

ROSE was repeated to make a decision for further examinations when access to the lesion was not satisfactory and an additional approach was considered to be possible. We calculated the effect of repeated ROSE on the diagnostic yield of peripheral lung cancer by fluoroscopy-guided bronchoscopy and found that a diagnostic improvement of 89.4% was attained by the first ROSE and 3.2% by the second ROSE (Table 4). Repeated ROSE improved diagnosis in only five of 107 examinations.

DISCUSSION

Bronchoscopic examination with fluoroscopic guidance is often used to obtain a diagnostic specimen of lung nodules. However, most reports have shown relatively low accuracy of diagnosing peripheral lesions by bronchoscopy.[10–12] Bandoh et al.[8] reported refined accuracy up to 91% by combining multiplanar reconstruction images and ultra-fast Papanicolaou staining. They used a historical control for comparison and multiplanar images for another tool. Our study was designed to improve the bronchoscopic diagnosis of peripheral malignant lesions by introducing only ROSE and was performed prospectively in routine bronchoscopic examinations. Therefore, more precise analysis could be performed to estimate ROSE's effectiveness. Our result shows that diagnostic sensitivity of peripheral malignant lesions was improved from 74.4% to 90.3% with ROSE only.

To obtain rapid diagnosis during bronchoscopy, the staining method should be convenient and fast and should present suitable coloring for diagnosis. Several staining methods are applied in ROSE.[8,14,15] We selected rapid Shorr staining for ROSE that we established recently[9] because it is simple, rapid, and similar in coloring to Papanicolaou staining, which is familiar to cytoscreeners and cytopathologists. Additionally, rapid Shorr staining requires only a small area for staining. Rapid Shorr staining is reliable, with low false-positive and false-negative rates.

To improve sensitivity, a method for obtaining additional samples should be carefully determined. When another visible bronchus could be a suitable path to the lesion, we selected this path. When the visible route to the lesion could not be improved, we changed the method for approaching to lesions to TBNA, ultra-thin bronchoscopy, or washing. Comparison among the methods indicates that TBNA and ultra-thin bronchoscopy were most effective in the approach through the same bronchus. In the approach through different bronchi, curetting and biopsy were effective for diagnosis, whereas TBNA was a good alternative (Table 3). Therefore,

TABLE 2. Results of bronchoscopic examinations with ROSE

ROSE	Final diagnosis	Diagnosis by conventional samples	Diagnosis by additional samples	Diagnosis by different examinations
Negative	279			
Malignant	154	26	80	48
Benign	113	13	2	98
Unknown	12	0	0	12
Positive suspected	21			
Malignant	17	10	4	3
Benign	4	1	0	3
Unknown	0	0	0	0
Positive	357			
Malignant	357	357	0	0
Benign	0	0	0	0
Unknown	0	0	0	0

ROSE, rapid on-site cytopathologic examinations.

TABLE 3. Methods of additional sampling for diagnosing malignant lesions

	Tested lesions	Sole positive	Positive
Brushing	16	0 (0.0%)	4 (26.7%)
(from other branch)	4	0 (0.0%)	1 (25.0%)
Curetting and forceps	101	33 (32.7%)	51 (50.5%)
(from other branch)	14	12 (85.7%)	13 (92.9%)
TBNA	35	16 (45.7%)	25 (71.4%)
(from other branch)	7	4 (57.1%)	6 (85.7%)
Washing	29	3 (10.3%)	12 (41.4%)
(from other branch)	4	1 (25.0%)	2 (50.0%)
Forceps with ultra-thin bronchoscope	20	14 (70.0%)	20 (100%)
Washing with ultra-thin bronchoscope	16	0 (0.0%)	11 (68.8%)

TABLE 4. Diagnostic yield of malignant lesions by repeated ROSE

ROSE	Bronchoscopic examinations	Additional examination	Diagnostic yield	Accumulated sensitivity
0	657		393	74.4%
1	657	214	79	89.4%
2	126	94	3	90.0%
3	20	12	2	90.3%
4	1	1	0	90.3%

ROSE, rapid on-site cytopathologic examinations.

alternative routes or methods such as TNBA or ultra-thin bronchoscopy should be considered when ROSE is not diagnostic. We do not recommend brushing and washing.

It has been reported that the size of the lesion has negative correlation to the sensitivity of bronchoscopy. Our results also showed low sensitivity for small lesions (≤2 cm). Surprisingly, however, improvement of diagnostic yield by ROSE was more prominent in diagnosing small lesions (Figure 1*B*). We analyzed the relationship between the size of lesions and the methods by which diagnosis could be made with additional samples. There was no distinct difference in frequency of usage of each method and its ability to yield additional diagnoses between the small and large lesions. Therefore, the reason why diagnostic yield improved more in smaller lesions is not known. One possible explanation is poor fluoroscopic targeting for smaller lesions in bronchoscopy. We used biplane fluoroscopy, but not CT, to determine whether the tip of sampling tools reached the lesions. It is reasonable that the error in targeting by this method is greater for small lesions than for large lesions. ROSE may have improved diagnostic yield partly by correcting the error in targeting.

There are several factors other than the size of tumors related to diagnostic yields. The experience of the examiners relates to the diagnostic sensitivity of bronchoscopic examinations.[16] The location of the lesion, histology type, and visibility under fluoroscopy can influence the yield. We analyzed the relationship between these factors and diagnostic yield. Experience of examiners, location of the lesion, and fluoroscopic visibility of lesions showed some relation to the diagnostic yield. However, improvement of diagnosis by ROSE was similarly observed for all examiners. Diagnostic yield of the lesions in the upper lobe and S6 was relatively low. However, we did not observe a clear difference of improvement by ROSE by location. Examinations for poorly

visible lesions under fluoroscopy showed low sensitivity compared with clearly visible lesions. The improvement by ROSE was slightly higher in the examinations for poorly visible lesions, although not statistically significant. Comparison among histology types of the lesions showed little difference in sensitivity and improvement by ROSE. We encourage the use of ROSE for diagnosing peripheral lesions, especially those of small size, regardless of their location, fluoroscopic visibility, or experience of the examiners.

We usually performed curetting and forceps biopsy only once before ROSE. Although repeated curetting and biopsy were thought to improve sensitivity, we repeated the collection of specimens only in negative ROSE cases, including false negatives. We performed additional examinations for only 214 cases with ROSE and showed an increased sensitivity by 14.9% instead of performing repeated curetting and biopsy in most of the 657 cases without ROSE. ROSE enabled us to avoid unnecessary examinations, even including false-negative cases. Considering the low effectiveness of repeated ROSE, single ROSE is recommended. Recently, CT screening and positron emission tomography have been experimentally introduced for the early detection of lung cancer.[16–18] We expect to diagnose peripheral lung nodules more safely and accurately in the future. The combination of ROSE with fluoroscopy-guided bronchoscopy is encouraged as a conventional method to enhance its safety and sensitivity.

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Usefulness of ultrathin bronchoscopy in diagnosis of lung cancer

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Summary Although ultrathin bronchoscopes are suggested to have comparable abilities to conventional bronchoscopes in diagnosing peripheral lung lesions, how to introduce ultrathin bronchoscopes into bronchoscopic examination is still to be determined. In our first study, 35 patients with peripheral lung lesions underwent ultrathin followed by conventional bronchoscopy to compare their diagnostic abilities. The diagnostic rate was 54.3% in conventional bronchoscopy alone, 60.0% in ultrathin bronchoscopy alone, and 62.8% in the combination of the two. In the next study, we introduced a rapid cytology test of the material obtained in conventional bronchoscopy. When malignant cells were not detected in the material by the rapid cytology, ultrathin bronchoscopy was immediately conducted. Thirty-two patients with negative rapid cytology were enrolled in this study. Ultrathin bronchoscopy resulted in diagnostic materials in 59.3% of these cases. Ultrathin bronchoscopes showed better access to the lesions than a brush or a curette introduced through conventional bronchoscopes. We conclude that ultrathin bronchoscopes have a comparable ability to conventional ones in diagnosing peripheral lung cancer even when used alone, and become a good complement to conventional ones by introducing the rapid cytology test.

1. Introduction

Diagnosis of peripheral lung lesions can be problematic for chest physicians. Bronchoscopy is a first choice of examination to obtain materials for cytological and histological diagnosis, but does not always result in a final diagnosis. Use of bronchoscopes with an outer diameter of 3 mm or less are called ultrathin broncoscopes and came into use in the 1980's [1,2]. Because of the lack of a built-in channel in their first generation, these bronchoscopes were used only to observe peripheral airways [2–7]. Afterward, ultrathin bronchoscopes with a built-in channel were developed and enabled brushing, biopsy, and bronchoalveolar lavage through the channel [8–13]. However, until recently most usage had been limited to infants or treatment of inflammatory diseases [6–8,10–12], and the reports on the diagnosis of lung cancer with ultrathin bronchoscopes has been limited [5,9,13]. The newest ultrathin bronchoscope, XP40 (Fig. 1), has a much wider range of movement of the tip, and a specialized forceps for biopsy, FD56D, has been developed. With

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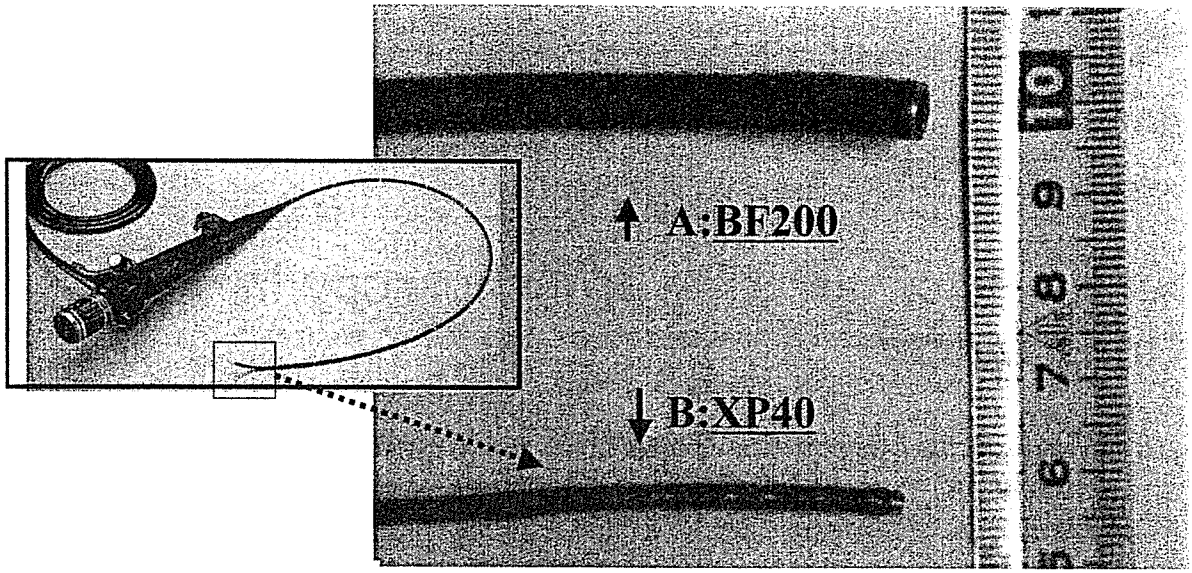

Fig. 1 A comparison of bronchoscopes. (A) conventional bronchoscope (B) ultrathin bronchoscope.

these developments, it has been suggested that the diagnostic abilities of ultrathin bronchoscopy for peripheral lung lesions has been improving. In this paper, we report on the results of two independent studies. In the first study, we compared the diagnostic rates between ultrathin and conventional bronchoscopy. In the next study, we applied a rapid cytology test, which we have recently established, to bronchoscopic examination, and tested the usefulness of XP40 as a complement to conventional bronchoscopy [14].

2. Patients and methods

2.1. Comparison between conventional and ultrathin bronchoscopy (Study A)

Among the patients who underwent bronchoscopy under fluoroscopic guidance in our hospital in 2000, 35 patients who had peripheral lung lesions that were small in size or located in the segment such as S^1, S^2, S^{1+2}, and S^6 where the approach with conventional bronchoscopes was considered difficult in general were subjected to the study. The median age was 64 years (range, 39–83 years); 19 patients were men and 16 patients were women. The median diameter of tumor was 21.7 mm (range, 10–40 mm).

Under local anesthesia with 2% lidocaine, bronchoscopic examination was initiated using an ultrathin bronchoscope, XP40 (Olympus Optical Co., Tokyo), with an outside diameter of 2.8 mm and a channel diameter of 1.2 mm. In succession, we performed the examination with one of the following conventional bronchoscopes, P200, P240, BF200, or BF240 (Olympus Optical Co., Tokyo), (outside diameters are 5.3 mm in P200 and P240, and 6.3 mm in BF200 and BF240; the channel diameters are 2.0 mm in all bronchoscopes). Brushing or curetting was done to obtain the materials for cytological examination; biopsy with forceps was done to obtain the materials for histological examination. The materials for both cytological and histological examinations were independently obtained in conventional and ultrathin bronchoscopy.

2.2. Rapid cytology test

Recently, we have developed a new method of the rapid cytology, Rapid Shorr stain [14]. Rapid Shorr stain is a modification of Gill–Shorr staining, and the staining can be completed within 2 min. Briefly, it is a combination of staining with hematoxylin solution and with modified Shorr's solution. Rapid Shorr stain requires only limited space, and therefore can be performed at the compartment for bronchoscopy. By introducing the rapid cytology using rapid Shorr stain into bronchoscopic examination, it became possible for us to perform an additional examination to obtain material from the tumor just after conventional bronchoscopic examination when rapid cytology testing of the material obtained from the standard examination was negative. We have performed the rapid cytology test almost routinely in the patients who were suspected of having lung cancer and whose lesion was difficult to approach with conventional bronchoscopy.

2.3. Combination of conventional and ultrathin bronchoscopy with the rapid cytology (Study B)

Among the patients who underwent conventional bronchoscopy under fluoroscopic guidance in our hospital from April till December of 2001, 32 patients had negative rapid cytology. The median age was 61 years (range, 35–82 years); 18 patients were men and 14 patients were women. The median diameter of the tumor was 24.4 mm (range; 12–55 mm). We performed ultrathin bronchoscopy on these patients to test the usefulness of ultrathin bronchoscopy as a complement of conventional brochoscopy. Immediately after conventional bronchoscopy, the presence or absence of malignant cells was determined by rapid cytology test using a part of the material. Biopsy by conventional bronchoscope was done in parallel with rapid cytology test, independent of the results of the rapid cytology. When malignant cells were present, the examination was completed only with conventional bronchoscopy. In contrast, when malignant cells were not detected, ultrathin bronchoscopy was added just after biopsy with a conventional bronchoscope.

2.4. Bronchoalveolar lavage with an ultrathin bronchoscope

Bronchoalveolar lavage was performed when possible. After biopsy, sterile saline of 10 ml was injected into the drainage bronchus of the lesion through the channel of XP40, and the recovered saline was subjected to cytological examination.

3. Results

3.1. Diagnostic rate of ultrathin bronchoscopy

Final diagnosis consisted of 23 primary lung cancers, 1 metastatic lung cancer, 3 pulmonary tuberculosis, and 1 mycobacterium avium complex disease. Final diagnosis wasn't determined in residual seven patients. The imaging, including chest computed tomography (CT), suggested that the lesions without final diagnosis were non-specific inflammatory processes, and most of these lesions showed a tendency to resolve during follow up. Twenty-two of 35 patients were diagnosed by either form of bronchoscopy, and therefore the overall diagnostic rate was 62.8%. Ultrathin bronchoscopy led to a diagnosis in 21 cases, and the diagnostic rate was 60.0%. Three of these cases were diagnosed only by ultrathin bronchoscopy. On the other hand, conventional bronchoscopy contributed to a diagnosis in 19 cases, and the diagnostic rate was 54.3%. One patient was diagnosed only by conventional bronchoscopy. Six patients who had not been diagnosed bronchoscopically were diagnosed by percutaneous needle lung biopsy or open lung biopsy.

3.2. Diagnosis by the combination of conventional and ultrathin bronchoscopy (Study B)

Additional ultrathin bronchoscopy was performed in 32 patients with negative rapid cytology. Fig. 2 shows the distribution in the lung of the lesions in this study. Papanicolaou stain after all bronchoscopic examination revealed that there were seven

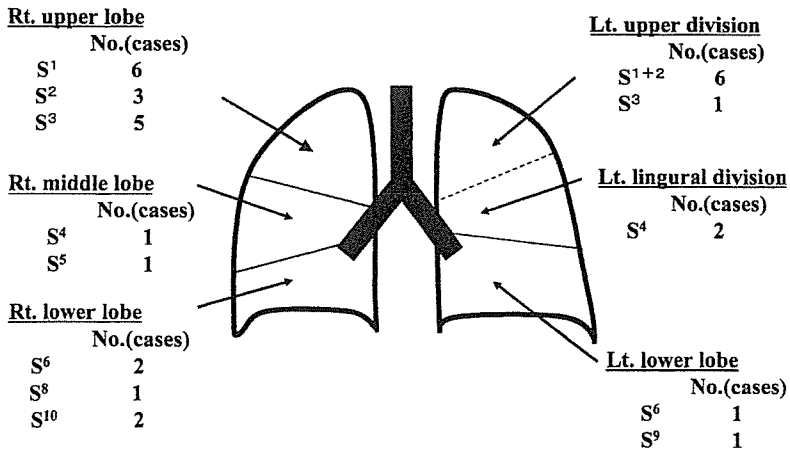

Fig. 2 Location of tumors in study (B).

false negative cases in rapid cytology. In contrast, there was no false positive diagnosis for rapid cytology. Final diagnosis consisted of 24 primary lung cancers, 2 metastatic lung cancers, 1 malignant lymphoma, 4 pulmonary tuberculoses, and 1 pneumonia. Twenty-two of 32 patients were diagnosed by either form of bronchoscopy, and therefore the overall diagnostic rate was 68.8%. Ultrathin bronchoscopy led to diagnosis in 19 cases, and diagnostic rate was 59.3%. On the other hand, conventional bronchoscopy led to diagnosis in nine cases, and the diagnostic rate was 28.1%. Thirteen patients (40.6% of the total 32 patients) were diagnosed only by additional ultrathin bronchoscopy. Bronchoalveolar lavage using an ultrathin bronchoscope was performed in 19 patients, and malignant cells were detected in 7 patients. In two patients, only bronchoalveolar lavage cytology was positive for malignant cells. Final diagnosis of 10 patients who could not be diagnosed by bronchoscopy was made by percutaneous needle lung biopsy or open lung biopsy.

4. Discussion

The improvement of ultrathin bronchoscopes, especially with the integration of a built-in channel, made it possible to perform brushing cytology, biopsy, and bronchoalveolar lavage utilizing the channel. Whereas most of the reports on ultrathin bronchoscopes so far have dealt with infant diseases or diffuse pulmonary diseases [6–8,10–12], there are only a limited number of studies in which diagnostic ability for lung cancer was compared between ultrathin and conventional bronchoscopy. Rooney et al. reported 17 patients examined by conventional and ultrathin bronchoscopy, type 3C40 [13]. Whereas biopsy and brushing cytology were done with a conventional bronchoscope, only brushing cytology was done with an ultrathin bronchoscope in their study. They concluded that ultrathin bronchoscopy appeared to be a useful adjunct to conventional bronchoscopy in the diagnosis of peripheral lung lesions. However, the diagnostic rate of an ultrathin bronchoscopy in this report was only 29.4% (5/17) even when including only three cases of atypical cells obtained in ultrathin bronchoscopy. They reasoned that this low diagnostic rate with an ultrathin bronchoscope was because only brushing cytology had been done. It can be postulated that brushing instruments for ultrathin bronchoscopy may not have enough power to gather adequate cells for diagnosis. In our study, we always performed biopsy in ultrathin bronchoscopy, and the material for cytology was obtained by smearing the residual material from histological examination. Both cytological and histological approaches are needed for diagnosis in ultrathin bronchoscopy. It is noted that cytological examination was very useful in ultrathin bronchoscopy because sufficient material for histological examination could not always be obtained with FB56D. We conclude that ultrathin bronchoscopy has comparable ability to conventional bronchoscopy in diagnosing lung lesions even when used alone.

As shown in Fig. 3, XP40 can wind in more complicated fashion than conventional bronchoscopes and more than a brush or a curette introduced through conventional bronchoscopes. Even in comparison with a brush or a curette in conventional bronchoscopy, XP40 generally demonstrated a better approach to the lesions. This might partly explain the improved diagnostic rate by ultrathin bronchoscopy.

We don't suggest here that ultrathin bronchoscopy should replace conventional bronchoscopy in the diagnosis of peripheral lung lesions, because ultrathin bronchoscopes are fragile and FB56D forceps are both fragile and expensive. Moreover, it is clear that the forceps for conventional bronchoscopes can obtain more material than that for ultrathin bronchoscopes. One possible way to improve the diagnostic rate in ultrathin bronchoscopy is to obtain more material, and therefore to increase the frequency of biopsy. We think that three to five biopsies are realistic with XP40.

One possible additional use of ultrathin bronchoscopes is when malignant cells are not detected by rapid cytology during bronchoscopic examination as shown in this manuscript. We showed that overall diagnostic rate was improved when ultrathin bronchoscopy was introduced in this way. Locations of tumor diagnosed with only ultrathin bronchoscope were as follows: (lt. B^{1+2}: 4 cases, rt. B^2: 2, rt. B^3: 2, rt. B^4: 1, rt. B^5: 1, rt. B^8: 1, lt. B^4: 1, lt. B^6: 1). The upper lobes, especially B^1, B^2, and B^{1+2}, followed by B^6 were most frequent sites. Additionally, 9 out of 13 lesions that were diagnosed only by ultrathin bronchoscopy were located in the upper lobes. These results suggest that the introduction of ultrathin bronchoscopy based on the results of rapid cytology is especially useful in diagnosing the lesions in B^1, B^2, B^{1+2}, and B^6.

Rapid Shorr stain is a type of rapid cytological staining. Compared with other staining such as Riu stain and Diff-quik stain, rapid Shorr stain has advantages of shorter staining time, and in that cellular features after staining are similar to those

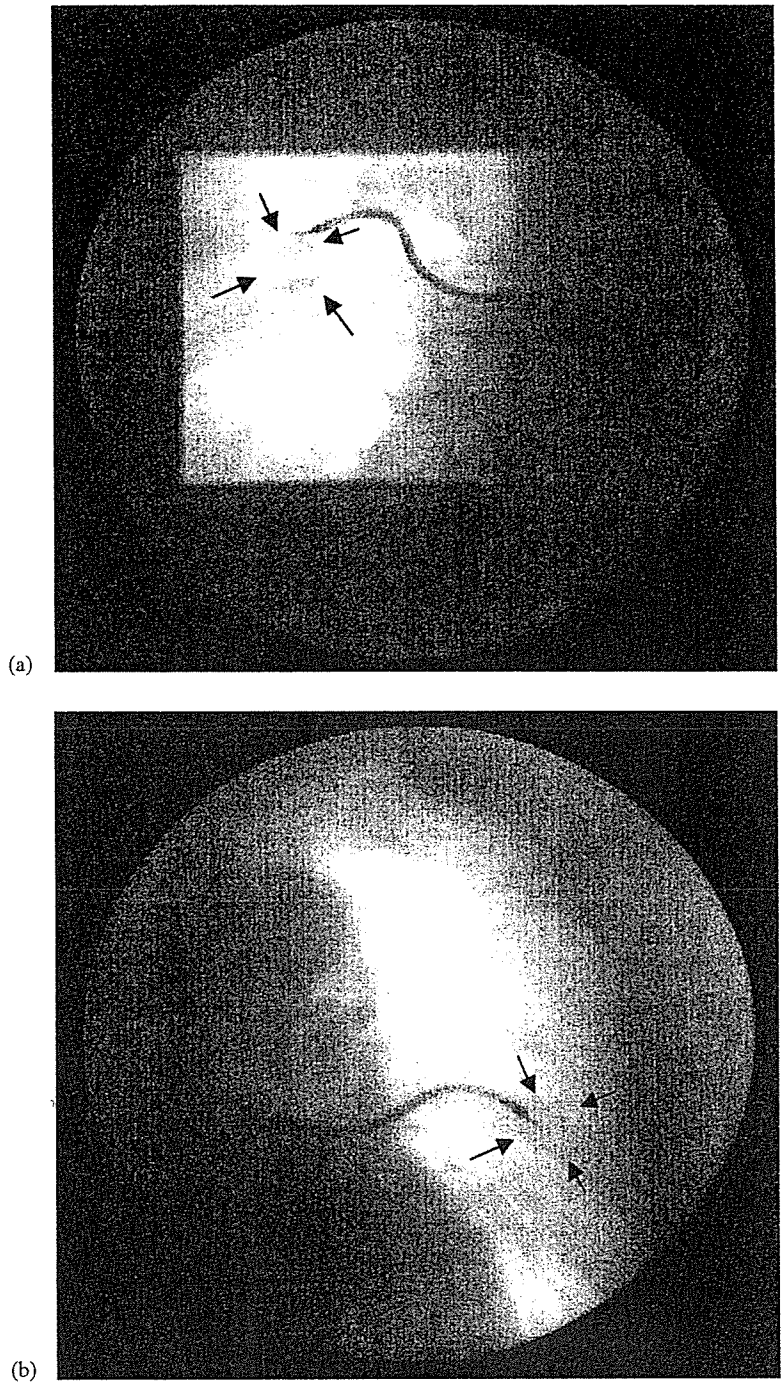

Fig. 3 Cases showing usefulness of ultrathin bronchoscopy. (a) ultrathin bronchoscope reached peripheral tumor of Rt B^2bi α. (b) ultrathin bronchoscope reached peripheral tumor of Lt B^6bii β.

in Papanicolaou stain. In our experience, sensitivity and specificity of rapid cytology were 84.6 and 100%, respectively, when compared to standard Papacicolaou stain that was done after the bronchoscopic examination [14]. We conclude that ultrathin bronchoscopy is a useful device for diagnosis of peripheral lung lesions, especially as a complement of conventional bronchoscopes.

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LETTER TO THE EDITOR

Severe myelotoxicity in a combination of gefitinib and vinorelbine

Gefitinib, a novel inhibitor of epidermal growth factor receptor tyrosine kinase (EGFR-TK), showed prompt symptom relief and disease stabilization of non-small cell lung cancer (NSCLC) with partial response rate of approximately 17% in recent phase II studies [1]. Since its mechanisms of action are different from those of cytotoxic agents, establishment of combination chemotherapy of gefitinib and cytotoxic agents is anticipated. However, the integration of gefitinib into the combination of cisplatin and gemcitabine or carboplatin and paclitaxel failed to show survival benefit in large-scale randomized phase III studies [2,3]. Vinorelbine has a relatively mild toxicity profile and can be used even for elderly and/or poor performance status patients, alone or in combination with the other cytotoxic agents [4]. Since vinorelbine is reported to show a strong synergistic antitumor effect when combined with gefitinib in preclinical studies [5,6], we conducted a pilot phase II study of gefitinib and vinorelbine combination chemotherapy for advanced NSCLC.

Patients who met the following criteria were enrolled into the study: age <75 years; histologically or cytologically confirmed NSCLC; stage IIIB or IV; no indication for radical thoracic irradiation; ECOG performance status (PS) of 0–2; preceding oral administration of gefitinib for at least 3 weeks without severe toxicity; adequate bone marrow function (leukocyte count $>3000\,mm^{-3}$, platelet count $>7.5\times10^4\,mm^{-3}$); adequate liver function (serum bilirubin <1.5 mg/dl, transaminases <twice the upper limit of normal); adequate renal function (serum creatinine <1.2 mg/dl). The primary endpoint of this study was evaluation of feasibility of this combination, and enrollment of 10 patients was planned. Fully informed consent was obtained from all patients before starting the therapy.

The treatment schedule was as follows: the administration of vinorelbine was added to oral gefitinib at a dose of $250\,mg/m^2$ per day. Vinorelbine was administered intravenously at a dose of $25\,mg/m^2$ on days 1 and 8 every 3 weeks. Toxicities were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC 2.0). When the patients experienced grade 4 hematological toxicity or grade 3–4 non-hematological toxicity, the dose of vinorelbine was to be reduced to $20\,mg/m^2$ in the next cycle. Treatment was to be discontinued when the patients experienced unacceptable toxicities or the disease showed progression. Between October 2002 and January 2003, four patients were enrolled into the study—Case 1: 46-year-old female; Case 2: 74-year-old female; Case 3: 74-year-old male; Case 4: 71-year-old male. Cases 1–3 had PS 2 and Case 4 had PS 0. Gefitinib monotherapy had been performed for 103, 25, 35, and 132 days, in Cases 1, 2, 3, and 4, respectively, before the administration of vinorelbine.However, subsequent enrollment was stopped because of severe toxicities observed in all of these patients, and the study was closed. Approximately at 1–2 weeks after the administration of vinorelbine, all four patients experienced severe myelotoxicity: life-threatening neutropenia occurred in all four cases and treatment-related death occurred in one case. Febrile neutropenia occurred in three patients. Grade 4 leukopenia, neutropenia, thrombocytopenia, and anemia occurred in 2 (50%), 4 (100%), 1 (25%), and 0 (0%) patients, respectively. The worst neutrophil counts during the first cycles were $48\,mm^{-3}$ (9th day), $44\,mm^{-3}$ (14th day), $0\,mm^{-3}$ (12th day), and $136\,mm^{-3}$ (16th day) in Cases 1, 2, 3, and 4, respectively. Neutropenia was generally short lasting in three cases reflecting possible response to granulocyte colony stimulating factor (G-CSF), whereas recovery from neutropenia was not observed in one patient (Case 3), who died of pneumonia on the 18th day of treatment. Grade 3 thrombocytopenia in Case 1 recovered rapidly without platelet transfusion. Non-hematological toxicity was rather mild: grade 2 epigastralgia in two patients (Cases 2 and 3), grade 1–2 diarrhea in three patients (Cases 1, 2, and 3), grade 2 mucositis in two patients (Cases 2 and 3), and grade 1 dermatitis in one patient (Case 2). There was no tumor regression. Two patients had stable disease (SD) and one patient had progressive disease (PD). Response could not be evaluated in one patient (Case 3) because of his early death.

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