Table 4 Nonhaematologic toxicity

	Nausea				Diarrhoea				Haematouria				Hepatotoxicity				alopecia		mucocitis				lethargy			
Dose level	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Phase I																										
1 ($n=3$)	2	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2	1	0	0	0	0	2	1	0	0
2 ($n=3$)	3	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2	1	1	0	0	0	3	0	0	0
3 ($n=2$)	1	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0	0	0	1	1	0
Phase II																										
2 (cycles = 50)[a]	30	12	4	0	12	7	0	0	5	0	0	0	12	0	0	0	17	8	5	0	0	0	24	7	0	0
1 (cycles = 8)	6	2	0	0	3	0	0	0	1	0	0	0	1	0	0	0	2	3	1	0	0	0	8	0	0	0
Total (cycles = 58)	36	14	4	0	15	7	0	0	6	0	0	0	13	0	0	0	19	11	6	0	0	0	32	7	0	0

[a]Three patients were from the phase I study.

of 22 patients, grade 4 neutropenia was observed and for these seven patients, the doses of CPT-11 and 254-S were reduced by one level for the next cycle. For phase II study, 50 cycles were administered at dose level 2 and eight cycles were administered at dose level 1. Finally, a total of 58 cycles were administered, with a median of two cycles per person (range: 1–6 cycles). Haematologic toxicities are summarised in Table 3. Grade 3 or 4 leukopenia, grade 3 or 4 neutropenia, grade 3 anemia, and grade 3 or 4 thrombocytopenia occurred in 43% (25 out of 58), 60% (35 out of 58), 26% (15 out of 58), and 14% (8 out of 58) of all cycles, respectively. The seven patients who had grade 4 neutropenia recovered after short-term therapy with rhG-CSF (median: 4 days; range: 3–9 days), and none of them developed febrile neutropenia. The median leukocyte count nadir occurred on day 16 (range: days 12–22). No patient required transfusion, including platelets or red blood cells. Nonhaematologoic toxicities are summarised in Table 4. There were no severe nonhaematologic toxicities. Only two patients received one cycle of chemotherapy because of PD. Treatment delays occurred in 12 patients (median: 7 days; range: 3–12 days). Occurrence of toxicity, including haematologic and nonhaematologic toxicity, did not appear to be associated with the cumulative dose.

Response

At dose level 1, one out of three patients achieved a clinical response, but there were no responders at dose level 3. In the phase II study ($n=22$), there were two CRs (9%) and 13 PRs (59%), for an overall response rate of 68% (95% CI: 49–84%).

In all 27 patients, there were two CRs (7%) and 14 PRs (52%), for an overall response rate of 59% (95% CI: 39–78%). Complete response occurred in patients with lung and Virchow's node metastasis as the measurable target lesions. Nine patients had NC (33%) and two patients had PD (7%) (Table 5). Among the 12 responders with recurrent disease, the median time to progression and median survival were 161 days (range: 61–711 days) and 415 days (range: 74–801 days). In one CR case, recurrence occurred at 534 days and the patient is now alive with disease at 801 days. Another CR case is now alive without disease at 711 days. In all, 27 cases, the median survival was 394 days (61–801 days).

Table 6 shows the responses stratified according to various clinical factors in all cases. The response rate was 57% (4 out of 7) and 60% (12 out of 20) for primary and recurrent cancer, respectively. The response rate was 53% (8 out of 15) and 67% (8 out of 12) for patients with and without prior treatment except for surgery, respectively. Among 22 patients with diseases outside the radiation field, 14 (two CRs and 12 PRs) achieved a clinical response (64%). Among five patients with disease inside the radiation field, two achieved a clinical response (PR: 40%). In the 10 patients less than 50 years old, the response rate was 80%, while

Table 5 Outcome of treatment

	Response				
Dose level	**CR**	**PR**	**NC**	**PD**	**Total**
1 ($n=3$)	0	1	2	0	1/3
2 ($n=22$)	2	13	5	2	15/22
3 ($n=2$)	0	0	2	0	0/2
Total ($n=27$)	2	14	9	2	16/27

CR = Complete response; PR = Partial response; NC = No change; PD = Progressive disease.

it was 47% in the 17 patients more than 50 years old. After chemotherapy, three out of four stage IVA patients received surgery plus chemoradiation and one received chemoradiation alone, and two out of three stage IVB patients received chemoradiotherapy and one received radiotherapy. Among the remaining 20 recurrent patients, one patient received chemoradiation, two patients received radiotherapy, and two had further chemotherapy after CPT-11 plus 254-S. When the response of measurable lesions was analysed, it was seven of 11 (64%) at the primary site, four of nine (44%) for lung, three of five (60%) for liver, and four of five (80%) for lymph nodes.

DISCUSSION

We conducted a phase I–II study of combination chemotherapy with CPT-11 plus 254-S and rhG-CSF support for advanced or recurrent cervical cancer. At dose level 3 (CPT-11/254-S: 60/80 mg m^{-2}), the first two patients developed grade 4 neutropenia and one of them had febrile neutropenia for 4 days. Accordingly, we defined the MTD for CPT-11/254-S as 60/80 mg m^{-2} and the RD for the phase II study as 50/80 mg m^{-2}. In the phase II study ($n=22$), 73% of the 22 patients experienced grade 3 or 4 neutropenia, although the seven patients who had grade 4 neutropenia recovered with rhG-CSF support and a good clinical response rate (68%) was achieved. Grade 3 or 4 neutropenia occurred in 60% (35 out of 58) of all cycles in phase II study, respectively. In all 27 patients, there were two CRs (7%) and 14 PRs (52%), for an overall response rate of 59% (95% CI: 39–78%).

Machida *et al* (2003) conducted a phase I study of this therapy for advanced or recurrent cervical cancer and concluded that (1) the DLT was neutropenia, 2) the MTD of CPT-11 (days 1, 8, and 15)/254-S (day 1) was 60/60 mg m^{-2}, and (3) the RD was 50/60 mg m^{-2}. Their data are concordant with ours. However, Oshita *et al* (2003) performed a phase I–II study in patients with

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.

REFERENCES

Bonomi P, Blessing JA, Stehman FB (1985) Randomized trial of three cisplatin dose schedules in squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. *J Clin Oncol* 3: 1079–1085

Brader KR, Morris M, Levenback C, Levy L, Lucas KR, Gershenson DM (1998) Chemotherapy for cervical carcinoma: factors determining response and implications for clinical trial design. *J Clin Oncol* 16: 1879–1884

Buxton EJ, Meanwell CA, Hilton C, Mould JJ, Spooner D, Chetiyawardana A, Latief T, Paterson M, Redman CW, Luesley DM (1989) Combination bleomycin, ifosfamide, and cisplatin chemotherapy in cervical cancer. *J Natl Cancer Inst* 81: 359–361

Ivrin WP, Price FV, Bailey H, Gelder M, Rosenbluth R, Durivage HJ, Potkul RK (1998) A phase II study of irinotecan (CPT-11) for patients with advanced squamous cell carcinoma of the cervix. *Cancer* 82: 328–333

Kameyama Y, Okazaki N, Nakagawa M, Koshida H, Nakamura M, Gemba M (1990) Nephrotoxicity of a new platinum compound, evaluated with rat kidney cortical slices. *Toxicol Lett* 52: 15–24

Kanazawa F, Koizumi F, Koh Y, Nakamura T, Tatsumi Y, Fukumoto H, Saijo N, Yoshida T, Nishio K (2001) *In vitro* synergistic interactions between the cisplatin analogue nedaplatin and the DNA topoisomerase I inhibitor irinotecan and the mechanism of this interaction. *Clin Cancer Res* 7: 202–209

Kato T, Nishimura H, Yakushiji M, Noda K, Terashima Y, Takeuchi S (1992) Phase II study of 254-S for gynecological cancer. *Jpn J Cancer Chemother* 19: 695–701

Long III HJ, Cross WG, Wieand HS, Webb MJ, Mailliard JA, Kugler JW, Tschetter LK, Kardinal CG, Ebbert LP, Rayson S (1995) Phase II trial of methotrexate, vinblastine, doxorubicin, and cisplatin in advanced/recurrent carcinoma of the uterine cervix and vagina. *Gynecol Oncol* 57: 235–239

Machida S, Ohwada M, Fujiwara H, Konno R, Takano M, Kita T, Kikuchi Y, Komiyama S, Mikami M, Suzuki M (2003) Phase I study of combination chemotherapy using irinotecan hydrochloride and nedaplatin for advanced or recurrent cervical cancer. *Oncology* 65: 102–107

McGuire WP, Blessing JA, Moore D, Lentz SS, Photopulos G (1996) Paclitaxel has moderate activity in squamous cervix cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 14: 792–795

Morris M, Brader KR, Levenback C, Burke TW, Atkinson EN, Scott WR, Gershenson DM (1998) Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix. *J Clin Oncol* 16: 1094–1098

Murad AM, Triginelli SA, Ribalta JC (1994) Phase II trial of bleomycin, ifosfamide, and carboplatin in metastatic cervical cancer. *J Clin Oncol* 12: 55–59

Nitta K, Yokokura T, Sawada S, Kunimoto T, Tanaka T, Uehara N, Baba H, Takeuchi M, Miyasaka S, Mudai H (1987) Antitumor activity of novel derivatives of camptothecin. *Gan To kagaku Ryoho* 14: 850–857

Omura GA, Blessing JA, Vaccarello L, Berman ML, Clarke-Pearson DL, Mutch DG, Anderson B (1997) Randomized trial of cisplatin *versus* cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 15: 165–171

Oshita F, Yamada K, Kato Y, Ikehara M, Noda K, Tanaka G, Nomura I, Suzuki R, Saito H (2003) Phase I/II study of escalating doses of nedaplatin in combination with irinotecan for advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol* 52: 73–78

Ota K, Oguma T, Shimamura K (1994) Pharmacokinetics of platinum in cancer patients following intravenous infusion of *cis*-diammine (glycolato) platinum, 254-S. *Anticancer Res* 14: 1383–1388

Ota K, Wakui A, Mashima N, Niitani H, Inuyama M, Ogawa I, Ariyoshi H, Yoshida O, Taguchi T, Kimura I, Katoh S (1992) Phase II study of a new platinum complex 254-S, *cis*-diammine (glycolato) platinum(II). *Jpn J Cancer Chemother* 19: 855–861, (in Japanese)

Papadimitriou CA, Dimopoulos MA, Giannakoulis N, Sarris K, Vassilakopoulos G, Akrivos T, Voulgaris Z, Vlahos G, Diakomanolis E, Michalas S (1997) A phase II trial of methotrexate, vinblastine, doxorubicin, and cisplatin in the treatment of metastatic carcinoma of the uterine cervix. *Cancer* 79: 2391–2395

Papadimitriou CA, Sarris K, Moulopoulos LA, Fountzilas G, Anagnostopoulos A, Voulgaris Z, Gika D, Giannakoulis N, Diakomanolis E, Dimopoulos MA (1999) Phase II trial of paclitaxel and cisplatin in metastatic and recurrent carcinoma of the uterine cervix. *J Clin Oncol* 17: 761–766

Robert TG, Mary BH, Taylor M, Michael T (2001) Cancer statistics 2001. *CA Cancer J Clin* 51: 15–36

Rose PG, Blessing JA, Gershenson DM, McGehee R (1999) Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 17: 2676–2680

Sasaki Y, Tamura T, Eguchi K, Shinkai T, Fujiwara Y, Fukuda M, Ohe Y, Bungo M, Horichi N, Niimi S, Minato K, Nakagawa K, Saijo N (1989) Pharmacokinetics of (glycolato-*O*,*O*′)-diammine platinum (II), a new platinum derivative, in comparison with cisplatin and carboplatin. *Cancer Chemother Pharmacol* 23: 243–246

Sekiya M (2002) Reports of the gynecologic tumor committee. *Acta Obstet Gynaecol Jpn* 54: 697–793, (in Japanese)

Sugeno K, Mizojiri K, Okabe H, Esumi Y, Takaichi M, Okada Y (1991) Study on the disposition of a new antineoplastic agent, *cis*-diammine (glycolate) platinum(254-S). *Iyakuhin Kenkyu* 22: 231–242

Suzumura Y, Kato T, Ueda R, Ota K (1989) Effect of treatment schedule on antitumor activity of glycolato-*O*,*O*′-diammine platinum(II), a new platinum derivative: comparison with *cis*-diamminedichloroplatinum(II). *Anticancer Res* 9: 1083–1088

Takeuchi S, Dobashi K, Fujimoto S, Tanaka K, Suzuki M, Terashima Y, Hasumi K, Akiya K, Negishi Y, Tamamaya T, Tanizawa O, Sugawa T, Umesaki N, Sekiba T, Aono T, Nakano H, Noda K, Shiota M, Yakushiji M, Sugiyama T, Hashimoto M, Yamaji A, Takamizawa H, Sonoda T, Takeda Y, Tomoda Y, Ohta M, Ozaki M, Hirabayashi K, Hiura M, Hatae M, Nishigaki K, Taguchi T (1991) A late phase II study of CPT-11 for uterine cervical cancer and ovarian cancer. *Gan To kagaku Ryoho* 18: 1681–1689

Thigpen T, Shingleton H, Homesley H, Lagasse L, Blessing J (1981) *Cis*-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix. A Phase II study of the Gynecologic Oncology Group. *Cancer* 48: 899–903

Thigpen T, Vance R, Khansur T (1994) Carcinoma of the uterine cervix: current status and future directions. *Semin Oncol* 21: 43–56

Thigpen T, Vance RB, Khansur T (1995) The platinum compounds and paclitaxel in the management of carcinomas of the endometrium and uterine cervix. *Semin Oncol* 22, (Suppl 12) 67–75

Tobina K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, Narabayashi M, Fukutomi T, Kondo H, Shimoyama M, Suemasu K, members of the Clinical Trial Review Committee of the Japan Clinical Oncology Group (1993) Toxicity grading criteria of the Japan Clinical Oncology Group. *Jpn J Clin Oncol* 23: 250–257

Verschraegen CF, Levy T, Kudelka AP, Lierena E, Freedman RS, Edwards CL, Hord M, Steger M, Kaplan AL, Kieback D, Fishman A, Kavanagh JJ (1997) Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. *J Clin Oncol* 15: 625–631

World Health Organization (1979) *Handbook for Reporting Results of Cancer Treatment*, Offset publication no. 48. Geneva: World Health Organization

Lung Cancer (2004) 46, 43–48

ELSEVIER

LUNG CANCER

IASLC

www.elsevier.com/locate/lungcan

Usefulness of ultrathin bronchoscopy in diagnosis of lung cancer

Suguru Yamamoto, Kiyonobu Ueno*, Fumio Imamura, Hiroto Matsuoka, Izumi Nagatomo, Yasuhide Omiya, Mana Yoshimura, Yoko Kusunoki

Department of Pulmonary Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan

Received 24 November 2003; received in revised form 16 March 2004; accepted 16 March 2004

KEYWORDS
Lung cancer;
Ultrathin bronchoscopy;
Conventional bronchoscopy;
Rapid cytology test;
Diagnosis;
BALF;
Rapid Shorr stain

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

*Corresponding author. Tel.: +81-6-6972-1181; fax: +81-6-6971-7636.
E-mail address: ueno-ki@mc.pref.osaka.jp (K. Ueno).

0169-5002/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2004.03.005

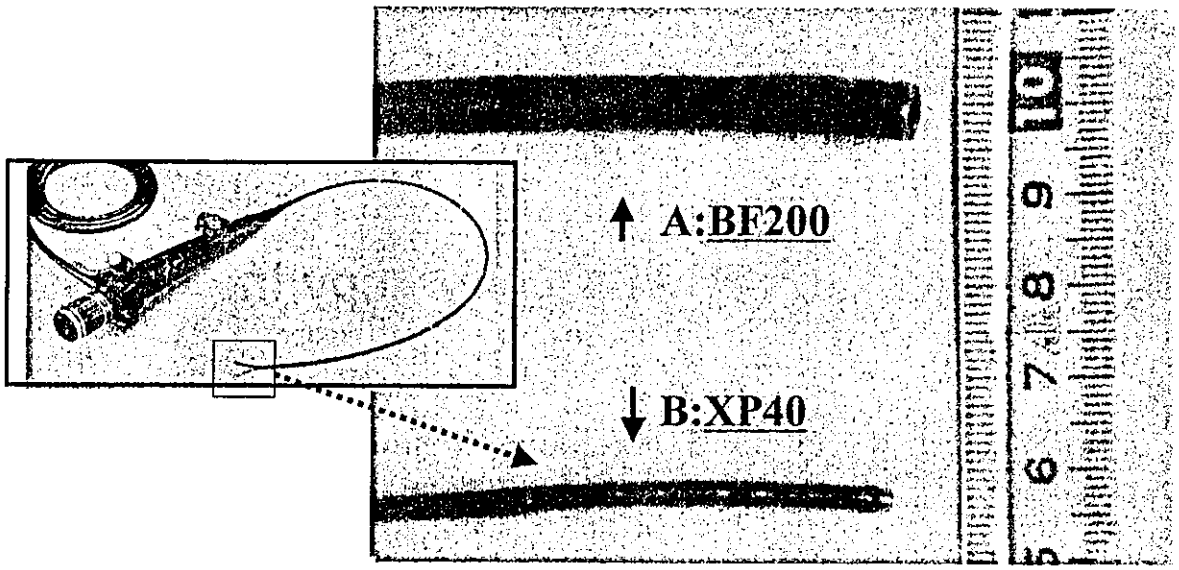


Fig. 1 A comparison of bronchoscopes. (A) conventional bronchoscope (B) ultrathin bronchoscope.

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

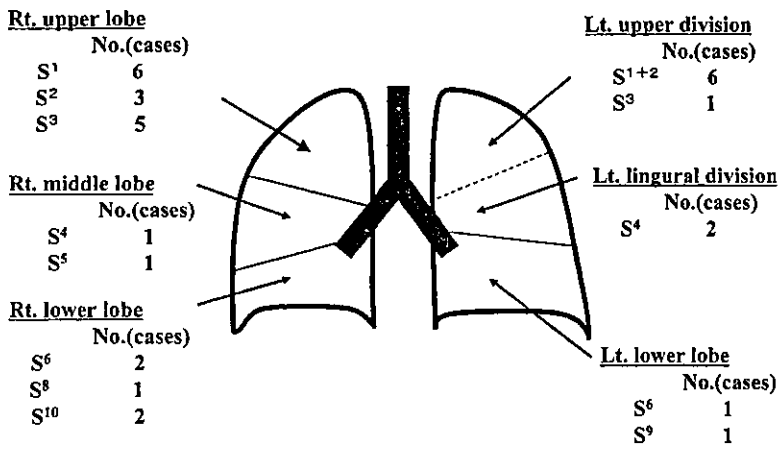


Fig. 2 Location of tumors in study (B).

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

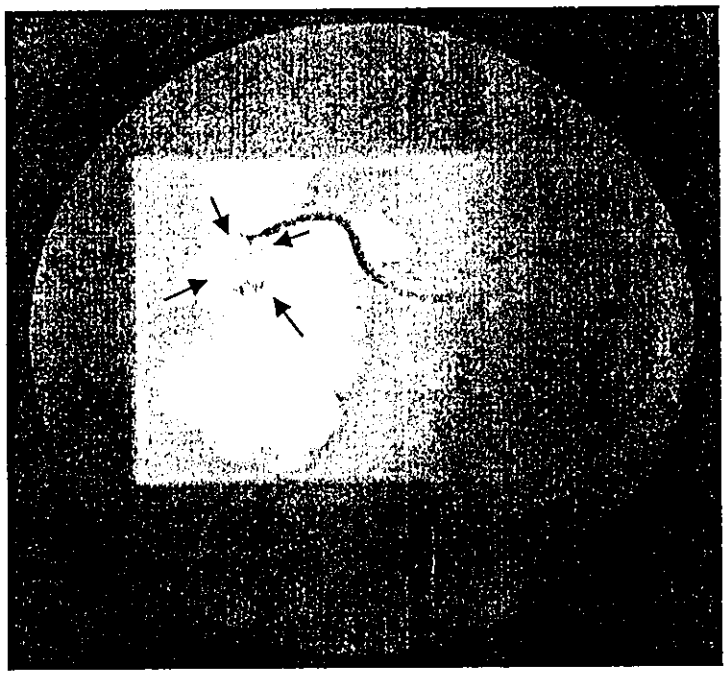
The improvement of ultrathin bronchoscopes, especially with the integration of a built-in channel, made it possible to perform brushing cytology, biopsy, and bronchoalveolar lavage utilizing the channel. Whereas most of the reports on ultrathin bronchoscopes so far have dealt with infant diseases or 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.

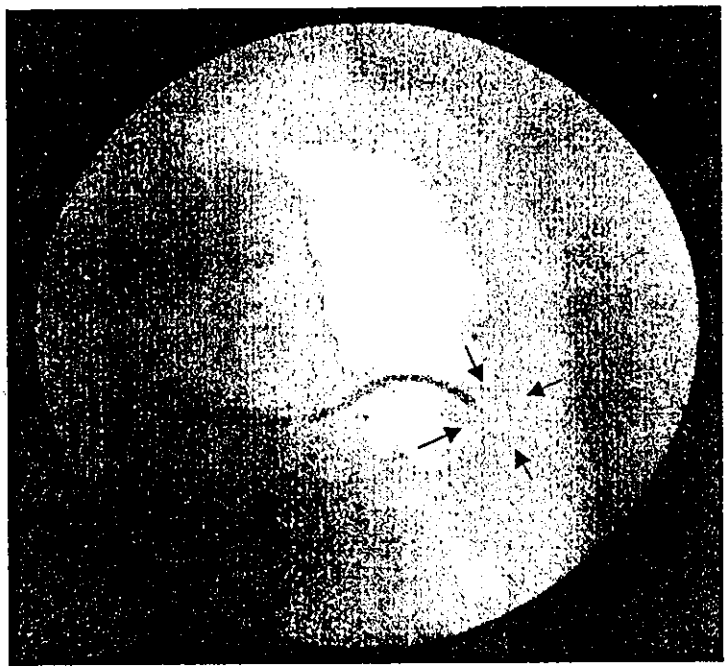
We don't suggest here that ultrathin bronchoscopy should replace conventional bronchoscopy in the diagnosis of peripheral lung lesions, because ultrathin bronchoscopes are fragile and FB56D forceps are both fragile and expensive. Moreover, it is clear that the forceps for conventional bronchoscopes can 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



(a)



(b)

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.

References

[1] Tanaka M. Advances and usefulness of ultra-thin bronchofiberscopes. Keio J Med 1996;45:296–300.

[2] Tanaka M, Satoh M, Kawanami O, Aihara K. A new bronchofiberscope for the study of diseases of very peripheral airways. Chest 1984;85:590–4.

[3] Wood RE. Clinical applications of ultrathin flexible bronchoscopes. Pediatr Pulmonol 1985;1:244–8.

[4] Tanaka M, Kawanami O, Satoh M, Yamaguchi K, Okada Y, Yamasawa F. Endoscopic observation of peripheral airway lesions. Chest 1988;93:228–33.
[5] Tanaka M, Kohda E, Satoh M, Yamasawa F, Kawai A. Diagnosis of peripheral lung cancer using a new type of endoscope. Chest 1990;97:1231–4.
[6] De Blic J, Delacourt C, Scheinmann P. Ultrathin flexible bronchoscopy in neonatal intensive care units. Arch Dis Child 1991;66:1383–5.
[7] Wood RE, Azizkhan RG, Lacey SR, Sidman J, Drake A. Surgical application of ultrathin flexible bronchoscopes in infants. Ann Otol Rhinol Laryngol 1991;100:116–9.
[8] Hasegawa S, Hitomi S, Murakawa M, Mori K. Development of an ultrathin fiberscope with a built-in channel for bronchoscopy in infants. Chest 1996;110:1543–6.
[9] Tanaka M, Takizawa H, Satoh M, Okada Y, Yamasawa F, Umeda A. Assessment of an ultrathin bronchoscope that allows cytodiagnosis of small airways. Chest 1994;106:1443–7.
[10] Kikawada M, Ichinose Y, Minemura K, Takasaki M, Toyama K. A study of peripheral airway findings using an ultrathin bronchofiberscope and bronchoalveolar lavage fluid with diffuse panbronchiolitis. Respiration 1998;65:433–40.
[11] Takizawa H, Tanaka M, Takami K, Ohtoshi T, Ito K, Satoh M, et al. Increased expression of inflammatory mediators in small-airway epithelium from tobacco smokers. Am J Physiol Lung Cell Mol Physiol 2000;278:L906–13.
[12] Mullins D, Livne M, Mallory Jr GB, Kemp JS. A new technique for transbronchial biopsy in infants and small children. Pediatr Pulmonol 1995;20:253–7.
[13] Rooney CP, Wolf K, McLennan G. Ultrathin bronchoscopy as an adjunct to standard bronchoscopy in the diagnosis of peripheral lung lesions. Respiration 2002;69:63–8.
[14] Omiya H, Imamura F, Takenaka A, et al. Establishment of new cytological staining method, rapid Shorr stain, and its application to bronchoscopic examination, submitted for publication.

Lung Cancer (2004) 45, 121–123

ELSEVIER

LUNG CANCER

IASLC

www.elsevier.com/locate/lungcan

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 >7.5×10^4 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.

0169-5002/$ - see front matter
doi:10.1016/j.lungcan.2004.01.006

Table 1 Toxicities

	Treatment		Toxicity grade				
	VNR (mg/m^2)	Gefitinib (mg per day)	WBC	Neu	Hb	Plt	FN
Case 1	25	250	G3	G4	G3	G3	G3
	20[a]	250[a]	G3	G4	G3	G0	G3
Case 2	25	250	G4	G4	G0	G0	–
	20[b]	–[b]	G2	G2	G1	G0	–
Case 3	25	250	G4	G4	G2	G4	G4
Case 4	25	250	G3	G4	G0	G0	G3
	–[b]	250[b]	G0	G0	G0	G0	–

G: NCI-CTC grade; VNR: vinorelbine; FN: febrile neutropenia.
[a] Second course with dose reduction of vinorelbine.
[b] Treatment after combination chemotherapy in the trial.

Toxicities of each case in this combination chemotherapy and in the treatment after the study are summarized in Table 1. One patient (Case 4) continued gefitinib monotherapy after the combination chemotherapy, and experienced no grade 3–4 hematological toxicities. Another patient (Case 2) received two cycles of vinorelbine monotherapy without gefitinib after combination chemotherapy. Vinorelbine alone also induced appreciable neutropenia but to a lesser degree (grade 0 in the first cycle and grade 2 in the second cycle). Case 1 received second cycle of the combination of gefitinib and vinorelbine with a dose reduction of vinorelbine to 20 mg/m^2 because the disease showed minor response. Although thrombocytopenia was not occurred in the second cycle, she again underwent severe neutropenia of 33 mm^{-3} in nadir count on 13th day. These results indicate that severe myelotoxicity induced by gefitinib and vinorelbine combination cannot be ascribed to the accidentally high susceptibility of the four patients to one of these drugs, but rather to this combination itself. This toxicity is unique in that it appeared almost selectively to neutrophils. In three patients, the worst neutrophil counts were under 100 mm^{-3}. In contrast, lymphocyte counts were stable in all cases. Anemia and thrombocytopenia were also mild. Typical clinical course is shown in Fig. 1.The mechanisms by which gefitinib and vinorelbine combination induces severe neutropenia are not

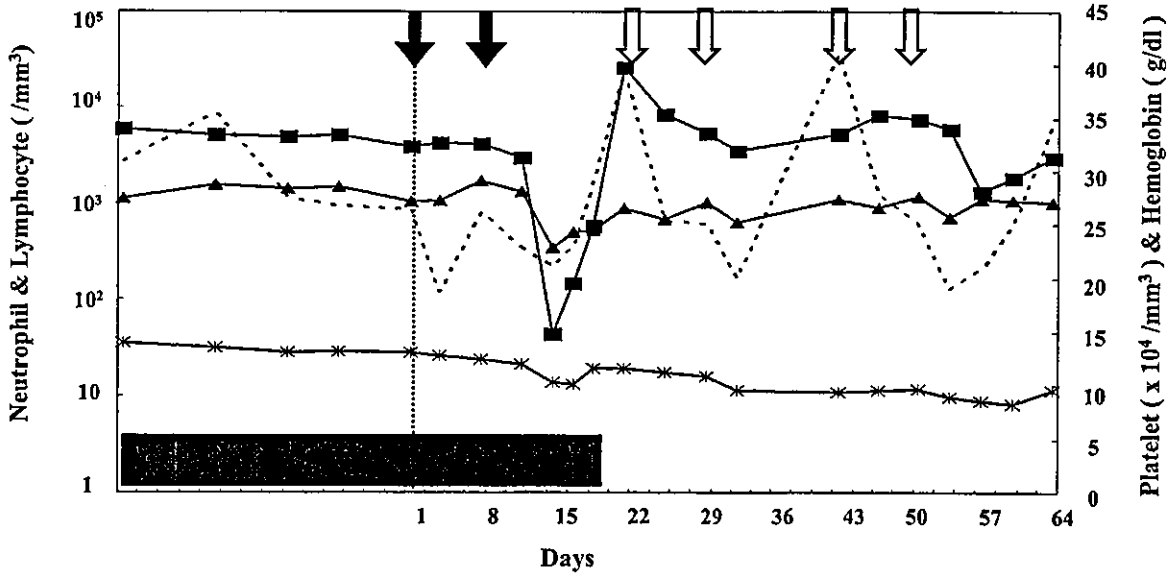


Fig. 1 Clinical course and hematocyte counts of Case 2 (74-year-old female): (▬) gefitinib 250 mg per day oral administration; (➡) intravenous vinorelbine 25 mg/m^2; (⇨) intravenous vinorelbine 20 mg/m^2; (■) neutrophil count; (▲) lymphocyte count; (···) platelet count; (✳) hemoglobin value.

known at present. Gefitinib is not myelotoxic even in higher doses in phase I study [7]. When combined with cisplatin and gemcitabine or with carboplatin and paclitaxel, gefitinib did not exert an appreciable increment of myelotoxicity [2,3]. Neutropenia is one of the common toxicities of vinorelbine, but usually well tolerated. Hence, severe myelotoxicity observed in the combination of gefitinib and vinorelbine is beyond the range of the toxicities of each drug. One possible explanation is drug interaction. Vinorelbine is metabolized in liver microsomes in the presence of NADPH-generating systems. The main enzyme involved is CYP3A4 [8]. Because CYP3A4 is also involved in the metabolism of gefitinib (personal communication), the metabolism of each drug may be modulated in the presence of the other. Serum concentration of vinorelbine may have been increased by the presence of gefitinib, resulting in the augmentation of the myelotoxicity of vinorelbine. However, other toxicities of vinorelbine such as decreased intestinal movement or thrombocytopenia did not seem to be intensified in gefitinib and vinorelbine combination. Therefore, the severe and selective neutropenia observed is not explained simply by drug interaction. Another explanation is the synergy of the two drugs on neutrophils alone. For this to happen, the precursor cells of neutrophils have to express EGFR. However, to date there is no supportive evidence for the expression of EGFR on hematocytes. The precursor cells of neutrophils may express unknown target molecules of gefitinib different from EGFR.

Molecular-targeted drugs may exert unpredictable severe toxicities because of their novel mechanisms of action. Life-threatening interstitial lung disease of gefitinib was already reported, for example, in Ref. [9]. In this study, we experienced another unpredictable severe toxicity of gefitinib combined with vinorelbine. Although clinical use of this combination cannot be recommended, analysis of the mechanism of neutropenia induced by gefitinib and vinorelbine combination is crucial for future use of gefitinib and other molecular-targeted drugs.

References

[1] Fukuoka M, Yano S, Giaccone G. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 2003;21:2237–46.

[2] Giaccone G, Johnson DH, Manegold C. A phase III trial of ZD 1839 (Iressa) in combination with gemcitabine and cisplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer (INTACT 1). Ann Oncol 2002;13(Suppl 5):2–3 [Abstract 4 O].

[3] Johnson DH, Herbst R, Giaccone G. ZD 1839 (Iressa) in combination with paclitaxel and carboplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer (NSCLC): results from a phase III clinical trial (INTACT 2). Ann Oncol 2002;13(Suppl 5):127–8 [Abstract 468 O].

[4] The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 1999;91:66–72.

[5] Sugiyama K, Yamashita K, Nishio K. Synergistic combined effect of vinorelbine and ZD 1839 (Iressa) in NSCLC cell lines which overexpress the phosphorylated EGFR and Erb2. Proc Am Assoc Cancer Res 2003;44:537 [Abstract 2737].

[6] Miyazaki M, Tamura K, Kurata T. Synergistic antitumor activity of ZD 1839 (Iressa), an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TK), in combination with vinorelbine in human lung cancer xenografts. Proc Am Assoc Cancer Res 2003;44:740 [Abstract 3720].

[7] Nakagawa K, Tamura T. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa, ZD 1839) in Japanese patients with solid malignant tumors. Ann Oncol 2003;14:922–30.

[8] Kajita J, Kuwabara T, Kobayashi H. CYP3A4 is mainly responsible for the metabolism of a new vinca alkaloid, vinorelbine, in human liver microsomes. Drug Metab Dispos 2000;28(9):1121–7.

[9] Inoue A, Saijo Y. Severe acute interstitial pneumonia and gefitinib. Lancet 2003;361:137–9.

Mana Yoshimura*, Fumio Imamura
Kiyonobu Ueno, Suguru Yamamoto
Department of Pulmonary Oncology
Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi
Higashinari-ku, Osaka 537-8511, Japan

Tsuyoshi Igarashi, Shinichiro Nakamura
NTT West Osaka Hospital
2-6-40 Karasuga-tsuji
Tennoji-ku, Osaka 543-8922, Japan

*Corresponding author
Tel.: +81-6-6972-1181
fax: +81-6-6971-7636
E-mail address: yosimura-ma@mc.pref.osaka.jp
(M. Yoshimura)

13 November 2003

ORIGINAL ARTICLE

Radiation Medicine: Vol. 22 No. 3, 163–167 p.p., 2004

A Single Institutional Subset Analysis of the WJLCG Study Comparing Concurrent and Sequential Chemoradiotherapy for Stage III Non-small-cell Lung Cancer

Takuhito Tada,* Kazuo Minakuchi,* Kaoru Matsui,** Hideki Kin,* Tomokazu Nishiguchi,* and Haruyuki Fukuda***

Purpose: To supplement findings of the West Japan Lung Cancer Group (WJLCG) study, treatment outcomes in our institution were reviewed from the perspective of radiation oncology.
Materials and Methods: Chemotherapy consisted of cisplatin (80 mg/m^2 on days 1 and 29), vindesine (3 mg/m^2 on days 1, 8, 29, and 36), and mitomycin (8 mg/m^2 on days 1 and 29). In the concurrent arm, radiation therapy began on day 2 with a dose of 56 Gy in 28 fractions over 6.8 weeks, with an interval of 10 days at 28 Gy. In the sequential arm, radiation therapy began on day 50 with a dose of 56 Gy in 28 fractions over 5.6 weeks, without an interval.
Results: Twenty-four patients in the concurrent arm and 25 patients in the sequential arm in our institution were eligible for the WJLCG study. In the concurrent arm, three patients could not receive the full dose of radiation therapy and 12 patients required interruption of radiation therapy for more than 4 days. The median survival time among per-protocol patients and in those with interruption or with incomplete radiation therapy was 28.9 months and 14.1 months, respectively (p=0.02). In the sequential arm, one patient could not receive the full dose of radiation therapy and none of the patients required such interruption. Local relapse and distant metastases as the first site of relapse occurred in 12 (11 in-field, 1 marginal) and five patients, respectively, in the concurrent arm, and in eight (7 in-field, 1 marginal) and 11 patients, respectively, in the sequential arm.
Conclusion: In the concurrent regimen, noncompletion or interruption of radiation therapy was frequent, and the prognosis of such patients was poor.

Key words: radiotherapy, chemotherapy, lung cancer, interruption

Introduction

In the treatment of patients with locally advanced non-small-cell lung cancer, a survival advantage is achieved by adding chemotherapy to radiation therapy.[1-3] To determine whether concurrent or sequential treatment with radiation therapy and chemotherapy improves survival for those patients, the West Japan Lung Cancer Group (WJLCG) performed a phase III study and concluded that concurrent treatment improved survival.[4] Though they provided several interesting findings, some issues concerning radiation oncology, such as frequency of interruption of radiation therapy or relapse sites in relation to the radiation fields, remained to be analyzed, since data analysis was mostly performed by medical oncologists in that study. In order to supplement findings of interest to radiation oncologists, data of the WJLCG study in our institution were reviewed, and several suggestive findings were newly pointed out.

Received November 12, 2003; revision accepted January 6, 2004.

Departments of *Radiology and **Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Disease
***Department of Radiology, Osaka City University Graduate School of Medicine
Reprint requests to Takuhito Tada, Department of Radiology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, JAPAN.

This paper was presented at the JRS meeting in April 2003.

Materials and Methods

Patients

Patients in both the concurrent and sequential arms, who entered the WJLCG study from our institution were eligible for the study. They were reviewed from the

Table 1. Patient characteristics

Characteristics	Concurrent therapy	Sequential therapy
No. of eligible patients	24	25
Age		
Range	42-75	39-74
Mean	60.1	60.1
Sex		
Male	21	23
Female	3	2
Histology		
Sq	13	10
Ad	9	12
La	2	3
10% weight loss	3	6
High LDH	1	6

Sq, squamous cell carcinoma; Ad, adenocarcinoma; La, large cell carcinoma.

perspective of radiation oncology.

Eligibility criteria for the WJLCG study are briefly presented here. Patients were required to have histologically or cytologically confirmed unresectable stage III non-small-cell lung cancer. Eligibility criteria included age younger than 75 years; measurable or assessable lesions; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; a required radiation field of less than one half of one lung; no prior chemotherapy, thoracic radiation therapy, or thoracic surgery; and no active concomitant malignancy. Patients were also required to have no abnormal hematologic, hepatic, renal, pulmonary, or cardiac functions.

Chemotherapy

The chemotherapy schedule of the WJLCG study is briefly presented here. Both in the concurrent arm and in the sequential arm, chemotherapy consisted of cisplatin (80 mg/m^2 on day 1), vindesine (3 mg/m^2 on days 1 and 8), and mitomycin (8 mg/m^2 on day 1). This chemotherapy was repeated every four weeks and was administered in two courses.

Radiation therapy

Thoracic irradiation was performed with 10 MV photons from a linear accelerator in our institution. (In the WJLCG study, 4 MV or higher photons were used.) In the concurrent arm, radiation therapy began on day 2 with a dose of 56 Gy in 28 fractions over 6.8 weeks, with an interval of 10 days at 28 Gy. In the sequential arm, radiation therapy began on day 50 with a dose of 56 Gy in 28 fractions over 5.6 weeks, without an interval. The radiation field was defined as the area that contained the primary tumor, a margin of 15 mm, the bilateral upper mediastinal lymph nodes, the subcarinal lymph nodes, and the regional enlarged lymph nodes. After initial irradiation with a dose of 40 Gy, off-cord (i.e., the spinal cord was outside the field) oblique boost fields were used.

RESULTS

Patient characteristics

Patients were enrolled in the WJLCG study between 1992 and 1994, and there were 315 eligible patients overall. Of these, 49 patients from our institution were reviewed in the current study. Twenty-four patients and 25 patients were treated in the concurrent and sequential arms, respectively.

The initial characteristics of the patients are listed in Table 1.

Survival

Nine patients survived for more than 5 years. The median survival time in the concurrent arm was 16.8 months, compared with 14.1 months in the sequential arm. The 2- and 5-year Kaplan-Meier survival rates in the concurrent arm were 33% and 17%, respectively, and those in the sequential arm were 36% and 20%, respectively (Fig. 1).

Among 22 patients with N3 disease, the median survival time and 5-year survival rate were 17.7 months and 26%, respectively.

Delivery and treatment toxicity

Patients with noncompletion and interruption of radiation therapy are listed in Table 2. Three patients in the concurrent arm and one in the sequential arm could not receive the full dose of radiation therapy. In the concurrent arm, radiation therapy was not completed because of infection in two patients and pulmonary

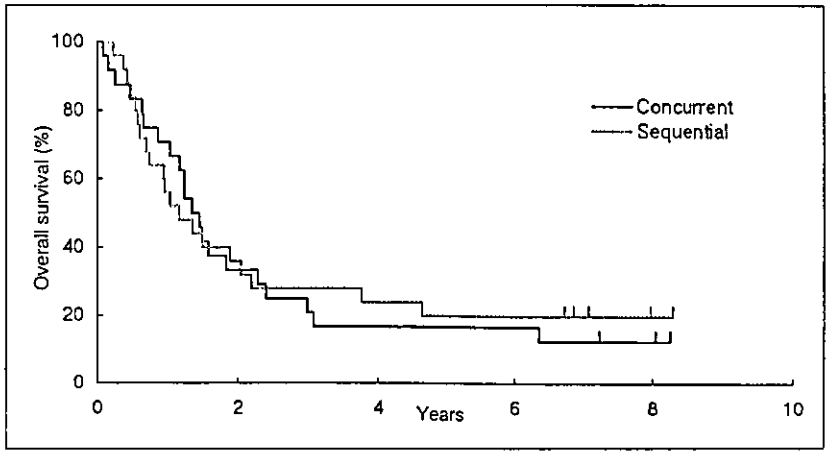


Fig. 1. Overall survival in patients according to treatment.

Table 2. Noncompletion and interruption of radiation therapy

	Concurrent therapy	Sequential therapy
No. of patients	24	25
Noncompletion	3	1
Interruption, days		
5-9	6	0
10-13	1	0
≥14	5	0
Per protocol	9	24

Per protocol: patients treated with no or less than 5-day interruptions.

hemorrhage in one patient. In the sequential arm, radiation pneumonitis caused radiation therapy to be stopped before completion in one patient.

Furthermore, in the concurrent arm, 12 patients required interruption of radiation therapy for more than 4 days, which delayed the completion of radiation therapy. Interruption from 5 to 9 days, 10 to 13 days, and more than 13 days was required in six, one, and five patients, respectively. Interruption was caused by myelosuppression, fever, and gastrointestinal toxicity in 11, two, and two patients, respectively. (Causes of interruption partly overlapped.) However, none of the patients required such interruption in the sequential arm.

In the concurrent arm, the median survival times among per-protocol patients (with no or less than 5-day interruption) and in those with interruption or with incomplete radiation therapy were 28.9 months and 14.1 months, respectively (generalized Wilcoxon, p=0.02; Fig. 2).

Relapse sites

Among patients who received the full dose of radiation therapy, local relapse and distant metastasis as the first site of relapse occurred in 12 and five patients, respectively, in the concurrent arm, and in eight and 11 patients, respectively, in the sequential arm. The first site of relapse is listed according to the respective histology in Table 3. Local relapse was subgrouped according to in-field relapse and marginal relapse, that is, relapse with respect to the radiation field. (Marginal relapse was defined as locoregional relapse outside the initial radiation field or at the edge of the radiation field.) In-field relapse and marginal relapse occurred in 11 patients and one patient, respectively, in the concurrent arm, and in seven patients and one patient, respectively, in the sequential arm. In the sequential arm, 10 of 11 distant metastases occurred within 1 year (median, 5.4 months). The 5-year in-field control rates in the concurrent arm and in the sequential arm were 36% and 52%, respectively (generalized Wilcoxon, p=0.22; Fig. 3).

Discussion

To improve the survival of patients with locally advanced non-small-cell lung cancer, the combination of chemotherapy and radiation therapy has been extensively investigated. The phase III study conducted by WJLCG was one such study.[4] Since the primary endpoint of the

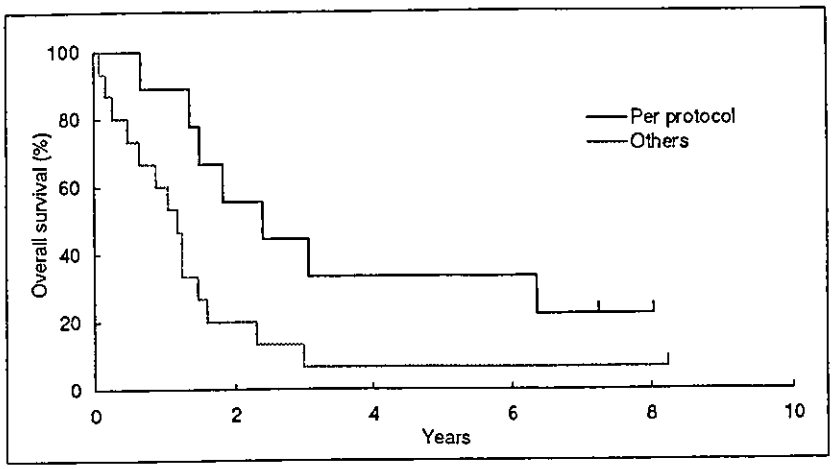


Fig. 2. Overall survival in per-protocol patients and others. Others were patients with interruption or with incomplete radiation therapy.

Table 3. First site of relapse

Histology	Concurrent therapy			Sequential therapy		
	Sq	Ad	La	Sq	Ad	La
No. of patients	12	7	2	10	11	3
Local relapse	9	3	0	6	1	1
Distant metastasis	1	2	2	2	8	1

Sq, squamous cell carcinoma; Ad, adenocarcinoma; La, large cell carcinoma.

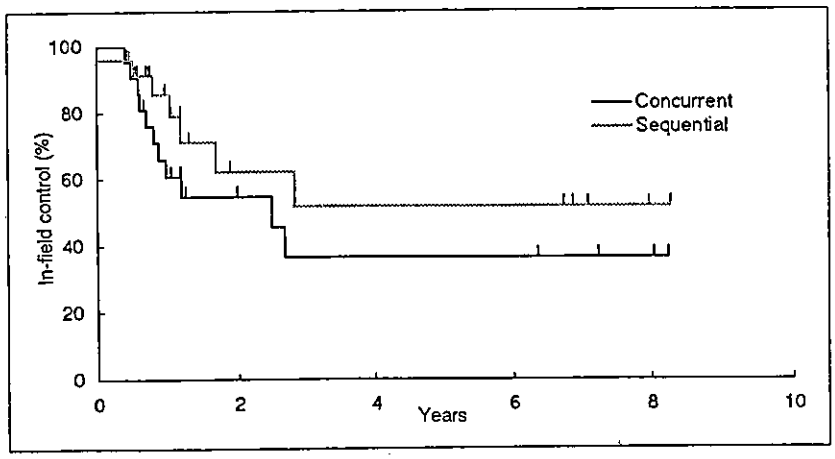


Fig. 3. In-field control in patients who received the full dose of radiation therapy.

phase III study was to determine whether concurrent or sequential treatment with radiation therapy and chemotherapy improves survival, the issue of radiation oncology was not a distinct focus. Though the current review was performed in only one institution, investigation from the perspective of radiation oncology indicated several suggestive findings, which may contribute to future studies.

In the current review, the sequential group showed a higher 5-year survival rate than the concurrent group. However, the difference was small and the sample size was also small. Therefore, we could not deny the conclusion of the WJLCG study that concurrent chemoradiotherapy improved survival. The high rate of per-protocol patients might have acted to improve long-term survival in the sequential group. On the other hand, in the concurrent group, there was a problem of frequent noncompletion or interruption of radiation therapy, and

survival among patients with noncompletion or interruption in radiation therapy was significantly poor. Cox *et al.* reported that interruption of radiation therapy decreases the long-term survival of patients with unresectable non-small-cell lung cancer in radiation therapy alone.[5] Results of the current study suggested that, in chemoradiotherapy, interruption of radiation therapy also decreased survival time. Furthermore, the frequency of interruption in the current study was much greater than that in the Radiation Therapy Oncology Group (RTOG) studies.[5] Furuse *et al.* conducted a pilot study of concurrent continuous radiation therapy and chemotherapy with use of cisplatin, vindesine, and mitomycin, and they often experienced irregular interruption of radiation therapy owing to neutropenic fever.[4] Therefore, a split-course fashion was used in the WJLCG study and was considered to help lessen the toxicity associated with concurrent radiotherapy and intensive chemotherapy. However, in the report on the WJLCG study, interruption of radiation therapy was not well discussed, and it was concluded that compliance with the protocol was acceptable. The toxicity of the concurrent regimen may be more serious than that evaluated by medical oncologists, and it is suggested that modification of chemotherapy or radiation therapy is required to decrease interruption.

Investigation of locoregional relapse should be performed separately from in-field relapse and marginal relapse. In the concurrent arm and sequential arm combined, marginal relapse occurred in only two patients, comprising 10% of locoregional relapse. The radiation field used in the current study was similar to that for patients with limited-stage small-cell lung cancer in our institution. In limited-stage small-cell lung cancer, 37% of the locoregional relapse was marginal relapse.[6] A prophylactic margin of the radiation field is considered less strictly necessary in non-small-cell lung cancer than in small-cell lung cancer. Relevant to this, 5-year survival was very poor in small-cell lung cancer patients with N3 disease. In contrast to the poor survival for small-cell lung cancer, the 5-year survival of 26% for patients with N3 disease was not less than that for other patients in the current review. The Southwest Oncology Group (SWOG) conducted a phase II study of concurrent cisplatin, etoposide, and chest radiotherapy, and reported a 5-year survival rate of 15% for non-small-cell lung cancer patients with N3 disease.[7] These results suggest that N3 disease of non-small-cell lung cancer does not have such a poor prognosis.

Even when the concurrent regimen was used, 5-year in-field control was only 36%, which was clinically assessed using chest X-ray or computed tomography. Since there is considerable room to improve local control, a more effective approach is awaited. For example, per-protocol delivery of radiation therapy by modifying chemotherapy, use of a new drug, or dose escalation using conformal radiotherapy might improve efficacy. The prescribed dose of 56 Gy was adopted based on the pilot study performed by Furuse *et al.*[4] When conventional radiation therapy is used, dose escalation is difficult in combination with the aggressive chemotherapy in the concurrent regimen. On the other hand, in the sequential arm, distant metastasis occurred in many patients, and those patients dropped out in the analysis of in-field control. Therefore, the 5-year in-field control rate of 52% was considered inaccurate.

In conclusion, the concurrent regimen was considered to be too toxic since noncompletion or interruption of radiation therapy was frequently observed. Marginal relapse comprised only 10% of locoregional relapse, and N3 disease was considered a substage with a not-so-poor prognosis. Since in-field control was insufficient even when the concurrent regimen was used, a more effective approach for local control is awaited.

References

1) 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. *BMJ,* 311: 899–909, 1995.
2) Pritchard RS, Anthony SP. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A meta-analysis. *Ann Intern Med,* 125: 723–729, 1996.
3) Schaake-Koning C, van den Bogaert W, Dalesio O, *et al.* Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med,* 326: 524–530, 1992.
4) 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,* 17: 2692–2699, 1999.
5) Cox JD, Pajak TF, Asbell S, *et al.* Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. *Int J Radiat Oncol Biol Phys,* 27: 493–498, 1993.
6) Tada T, Minakuchi K, Koda M, *et al.* Limited-stage small cell lung cancer: local failure after chemotherapy and radiation therapy. *Radiology,* 208: 511–515, 1998.
7) Albain KS, Crowley JJ, Turrisi AT 3rd, *et al.* Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol,* 20: 3454–3460, 2002.

Lung Cancer (2004) 46, 247–254

ELSEVIER

LUNG CANCER

www.elsevier.com/locate/lungcan

Retrospective analysis of the predictive factors associated with the response and survival benefit of gefitinib in patients with advanced non-small-cell lung cancer

Hiroyasu Kaneda, Kenji Tamura, Takayasu Kurata, Hisao Uejima, Kazuhiko Nakagawa, Masahiro Fukuoka*

Department of Medical Oncology, Kinki University School of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan

Received 5 February 2004; received in revised form 5 April 2004; accepted 15 April 2004

KEYWORDS
Gefitinib;
Non-small-cell lung cancer;
Prognostic factor;
Smoking index;
Female;
Performance status (PS);
Retrospective analysis

Summary

Background: The purpose of the study was to identify the potential predictive features associated with the response and survival benefit of gefitinib administration. We have retrospectively reviewed data of all patients who received a single regimen of gefitinib in our institution from August 1998 until July 2003.

Methods: Overall 101 patients with non-small-cell lung cancer (NSCLC) who have received a single use of gefitinib were analyzed. Potential factors associated with the response of gefitinib included smoking index, gender, histology, performance status (PS), number of pre-treatments, age and stage. Univariate analysis was performed for these strata by Fisher's exact test and multivariate analysis was then performed using the logistic regression model.

Results: The overall response rate was 19.8%. Univariate analysis revealed that significant predictive factors were associated with the response for 'adenocarcinoma', 'female', 'good PS' (0–1) and 'non-smoker' categories. Multivariate analysis limited the predictive factors associated with the response for 'female' ($P = 0.0032$), 'good PS' ($P < 0.02$) and 'non-smoker' ($P = 0.0417$). In survival analyses, 'female' ($P < 0.005$), 'good PS' ($P < 0.0001$), and a low level of the smoking index ($P < 0.05$) indicated significantly prolonged survival. Response and survival data in elderly patients were equivalent to those in younger patients. Adverse events (AEs) were generally mild and were almost always skin reactions and diarrhea. Interstitial lung disease (ILD) occurred in 4% of the group under observation.

Conclusions: Gefitinib provided clinical benefit for the following factors 'female', 'good PS' and 'non-smoker'. A low smoking index is reported as a novel predictive prognostic factor following a single regimen of gefitinib.

Abbreviations: NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; IDEAL-1, Iressa dose evaluated advanced lung cancer-1; PS, performance status; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; INTACT-1, Iressa NSCLC trial assessing combination treatment-1; INTACT-2, Iressa NSCLC trial assessing combination treatment-2

*Corresponding author. Tel.: +81 72 366 0221; fax: +81 72 360 5000.
E-mail address: mfukuoka@med.kindai.ac.jp (M. Fukuoka).

0169-5002/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2004.04.032

1. Introduction

Patients with advanced non-small-cell lung cancer (NSCLC) have a poor prognosis with 1–5% 5-year survival rates [1]. A recent meta-analysis demonstrated that platinum-based combination chemotherapy is currently considered to be the most effective treatment for advanced NSCLC, and these have improved the median survival time (MST) by 2 months and caused a 10% increase in 1-year survival rates [2]. As platinum-based chemotherapy improves survival and quality of life in advanced NSCLC patients, most patients will receive second line chemotherapy. With recurrence or progression, docetaxel has been approved as a second line chemotherapy treatment due to demonstrated survival benefit compared with best supportive care (BSC) or vinorelbine/ifosfamide [3,4]. Currently, there is no proven effective chemotherapy for patients previously treated with platinum-based and docetaxel therapies.

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because many types of cancer cells express or overexpress EGFR (including NSCLC, renal cell carcinoma and breast cancer) [5,6]. EGFR overexpression has been reported as a poor prognostic factor in many types of human solid tumors including NSCLC in several studies [7–9]. Currently, monoclonal antibodies that bind to the extracellular domain of EGFR and intracellular tyrosine kinase inhibitors have been developed [10,11]. Gefitinib is an orally active, selective EGFR tyrosine kinase inhibitor that blocks signal transduction pathways implicated in the proliferation, angiogenesis, invasion, metastasis and survival of cancer cells [12,13]. Several phase I trials demonstrated safety and tolerability of gefitinib in pretreated patients with solid tumors, in which trials an 11% response rate was seen in 100 patients with heavily pretreated advanced NSCLC [14]. On the other hand, in Japan, a phase I trial demonstrated five responders out of a total of 31 patients who all had adenocarcinoma of the lung [12]. To confirm anti-tumour activity and the safety profile of gefitinib, an international phase II study (IDEAL-1) and United States trial (IDEAL-2) were conducted as a second or third line treatment in patients with advanced NSCLC [15,16]. Patients enrolled in these studies were randomized into two different doses, 250 and 500 mg/day. These trials demonstrated that toxicity was mild and showed an encouraging response rate with an RR of 18.4 and 11.8% of patients in the 250 mg arm, respectively, and an improvement in disease related symptoms and quality of life were observed. The IDEAL-1 study has also confirmed that there were statistically significant differences in efficacy for 'adenocarcinoma' and 'female' using multivariate analysis. Two large randomized phase III studies [17,18], which are standard chemotherapy (cisplatin/gemcitabine or carboplatin/paclitaxel) with or without gefitinib, failed to demonstrate a survival benefit for advanced NSCLC patients as a first line chemotherapy. Although the results of the phase III studies were negative, gefitinib is still considered a promising molecular targeted agent as a new generation treatment in patients with advanced NSCLC. Information on the clinical prognostic factors following a single regimen of gefitinib should be helpful in finding which patients are likely to receive benefit, and in the development of a future treatment. Although the previous phase II trial (IDEAL) showed that several predictive factors were associated with the response to gefitinib, the population was essentially biased towards the young, with good performance status (PS) and conserved, good organ functions.

In this study, to find factors associated with an objective response and survival benefit of gefitinib, we retrospectively analysed patients who received a single regimen of gefitinib at our institute.

2. Methods

All patients with stage IIIB or IV NSCLC, who received a single regimen of gefitinib from August 1998 until July 2003 at the Kinki University School of Medicine, Osaka, were retrospectively reviewed. We evaluated patients who participated in clinical trials (phase I trial, phase II trial; IDEAL-1), or phase II trial for investigating surrogate gene therapy, and in 53 patients who were administered the drug after marketing (including elderly or poor performance status patients). Patients who received gefitinib as part of a compassionate use program were excluded. All patients were checked for age, gender, histology, Eastern Cooperative Oncology Group (ECOG), PS, stage, pre-treatment regimen, number of prior regimen, and smoking status before treatment of gefitinib. Smoking status was evaluated by the Brinkmann index; number of cigarettes per day multiplied by number of years. We analyzed the response, overall survival rate and the adverse effects of gefitinib, and investigated predictive factors associated with response and prognosis. The response was assessed using physical examination, biochemical profile, chest X-ray, chest computed tomography (CT), head CT or magnetic resonance imaging (MRI) scan, abdominal echo-graphic or abdominal CT scan, bone scinti-graph, bronchoscope, and was evaluated according to the response eval-

uation criteria in solid tumor (RECIST) [19]. The severity of all the adverse events (AEs) that related to gefitinib administration was assessed by the NCPCTC (version 2.0) grading system. The predictive factors associated with the response that were analyzed in this study were age, gender, PS, histology, stage, number of prior regimen and smoking status. Variables were tested for any possible relationship with the response to gefitinib, at first by univariate analysis, and subsequently by the application of a multivariate model. Response rates were compared between strata using Fisher's exact test. Logistic regression models were used to explore observed differences and identify baseline factors that may independently predict for response rates. The survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. *P*-values less than 0.05 were considered significant.

3. Results

3.1. Patient profiles

From August 1998 until July 2003 at our institute, a total of 105 patients, who were already cytologically or histologically diagnosed as NSCLC, were treated by a single regimen of gefitinib. Patients received gefitinib until disease progression or intolerable toxicity. Of these, 101 patients were evaluated as suitable for analysis; four patients were excluded from analysis because they received gefitinib as part of a compassionate use program. As shown in Table 1, the 101 patients included: 2 patients who received gefitinib at a once daily dose of 50 mg; single patients who each received 100, 225, 400, 525 and 700 mg, respectively; 89 patients who received 250 mg; and 5 patients who received 500 mg. In the phase I trial, we used an intermittent administration schedule with 14 days continuous dosing followed by 14 days off.

Table 1 Patient characteristics

	Number of patient ($N = 101$)
Phase I	7
50 mg	2
100 mg	1
225 mg	1
400 mg	1
525 mg	1
700 mg	1
Phase II (IDEAL-1)	11
250 mg	6
500 mg	5
Phase II (gene expression) (250 mg)	30
Post marketing (250 mg)	53

Table 2 Patient characteristics ($N = 101$)

	Number of patients
Age (year)	
Median (range)	62 (31–84)
<69	74
≥70	27
Gender	
Male	64
Female	37
Performance status	
0	15
1	62
2	17
3	7
Tumor histology	
Adenocarcinoma	81
Squamous	18
Large-cell	2
Stage	
III	18
IV	83
Previous treatment	
No treatment	5
Failed 1 previous chemotherapy regimens	53
Failed 2 previous chemotherapy regimens	34
Failed 3 previous chemotherapy regimens	9
Smoking (smoker:never-smoker)	55:46
Index[a] 0:1–999:1000	46:32:23

[a] Index: number of cigarettes per day multiplied by number of years.

Patient characteristics are shown in Table 2. The median age was 62 years (ranging from 31–84) and 74 patients (73.3%) were less than 69 years old. 63.4% of the patients were male, 76.2% had performance status (ECOG) 0–1, 80.2% had adenocarcinoma of which 83.2% had stage IV disease. Fifty-three patients had received one prior regimen, 43 had more than two prior regimens and only five had previously been untreated. 54.5% of them were smokers, and the non-smokers were almost all female. This study included patients