versus four-drug combinations showed severer toxicity in the four-drug arm with no improvement in survival.[19] A regimen of cisplatin and etoposide (PE) alternating with cyclophosphamide, doxorubicin, and vincristine (CAV) every 10–11 days at half the standard dose failed to reduce toxicity or improve survival compared with the standard PE alternating CAV regimen in a randomized trial.[20] Another randomized trial of cyclophosphamide, etoposide, and vincristine (CEV) given as needed to palliate symptoms, versus CEV given at fixed 3- to 4-week treatment intervals showed that patients randomized to receive chemotherapy as needed had a median interval between cycles of 5 weeks and received only 50% as much total chemotherapy as the patients randomized to the fixed schedule. Although the median survival times were equivalent between both arms, better symptomatic control was achieved with the fixed interval treatment.[21] Thus, these less intensive treatments than the standard treatment are not less toxic or useful for palliation.

The combination of carboplatin and etoposide has been one of the most frequently evaluated regimens in elderly patients with SCLC, and has yielded a response rate of 70–90% and a median survival of 8–10 months for ED and 12–15 months for LD with acceptable toxicity in phase II trials (Table 5).[22,23,25] Modification of the carboplatin dose based on creatinine clearance levels can be especially useful in elderly patients, because many of them have impaired renal function. As a result, this two-drug combination periodically repeated every 3- to 4-weeks has become standard treatment in this patient population (Evidence level, II).

Treatment of elderly patients with limited disease who are in good general condition

A retrospective review of 1208 patients (including 398 SCLC patients, 107 patients more than 70 years of age, 114 patients with PS 2 or higher, and 352 patients with body weight loss greater than 5%) in six EORTC clinical trials (including three for NSCLC, one for SCLC, and two for esophageal cancer) showed that age did not influence the frequency or severity of acute and delayed toxicity of thoracic radiotherapy.[27] Retrospective subset analysis of patients with limited SCLC who were treated with concurrent chemoradiotherapy in phase III trials showed that 80% of the patients 70 years of age or older completed the planned treatment, although hematological toxicity was severer in the elderly group than the younger group (Table 3).[15,16] Only patients with good general condition were included in these trials; 90% had PS 0–1 and 82% had less than 5% body weight loss in the one study,[16] and 84% had PS 0–1 in the other.[15] Thus, the standard chemoradiotherapy can be given to elderly patients in good general condition with PS 0–1, normal organ function and no comorbidity (Evidence level, IV).

Treatment for unselected elderly patients with limited disease

There are three phase II trials of concurrent chemoradiotherapy in this patient population. Although the chemotherapy cycles in these trials were reduced compared with the standard 4–6 cycles, the 5-year survival rates reached to 13–25% with manageable toxicity (Table 6).[28–30] Thus, a combination of full-dose thoracic radiotherapy and two cycles of chemotherapy may be the optimal treatment in unselected elderly patients with limited disease (Evidence level, III).

Discussion

It has been thought to be difficult to establish standard treatments for elderly patients with SCLC, because they form a heterogeneous population in terms of general condition and treatment outcome varies from report to report. However, by classifying studies on the treatment of this population into three types and characterizing subjects included in the studies, relatively consistent results were obtained. To select the optimal treatment for elderly patients, two groups needed to be considered separately: elderly patients in good general condition and all others. The former can be treated with the same strategy as younger patients with minor modifications, if any.

Among elderly patients, 30–50% have PS 2 or higher, and 60–80% have complications in major organs including the kidney, heart, and lung.[6,9–11] They have been treated with oral etoposide or combination chemotherapy at decreased doses or longer intervals. These less intensive treatments than the standard treatment, however, were not less toxic or useful for palliation in the elderly with decreased activity. By contrast, two-drug combination chemotherapy, including a combination of etoposide and carboplatin, produced response rates (RRs) and median survival times (MSTs) comparable to those of younger patients with

Table 5 Phase II trials for elderly or poor risk patients with small cell lung cancer

Authors (year)	Chemotherapy regimen (mg/m^2)	Number of patients	Age $\geqslant 70$ (%)	PS $\geqslant 2$ (%)	RR (%)	Grade 3–4 toxicty (%)	TRD (%)	MST (month)
Evans et al. (1995)[22]	Oral E (100 mg) days 1–7 Carbo (150) day 1	47	Median 69	30	71	Neutropenia (84) Thrombocytopenia (21) Stomatitis (2)	18	LD 14 ED 11
Matsui et al. (1998)[23]	Oral E (40) days 1–14 Carbo[a] day 1	38	100	34	81	Neutropenia (53) Thrombocytopenia (53) Infection (8)	5	LD 15 ED 9
Westeel et al. (1998)[24]	P (30) A (40) V (1) day 1 E (100) days 1, 3, 5	41	100	66	88	Infection (6) Emesis (9)	0	ED 11
Okamoto et al. (1999)[25]	E (100) days 1–3 Carbo[a] day 1	36	100	25	75	Neutropenia (86) Thrombocytopenia (50) Infection (5)	3	LD 12 ED 10
Samantas et al. (1999)[26]	Oral E (100 mg) days 1–12 Carbo (80) weekly	60	Median 66	59	32	Neutropenia (6) Thrombocytopenia (2) Infection (3)	3	5.5

Carbo, carboplatin; E, etoposide; ED, extensive disease; LD, limited disease; MST, median survival time; PAVE, cisplatin, doxorubicin, vincristine and etoposide; PS, performance status; RR, response rate; TRD, treatment-related death.

[a] Dose adjusted for creatinine clearance.

Table 6 Phase II trials of chemoradiotherapy for elderly or poor risk patients with limited small cell lung cancer

Authors (year)	Chemotherapy radiotherapy (Gy/fraction)	Number of patients	Age ⩾70 (%)	PS ⩾2 (%)	RR (%)	Grade 3–4 toxicty (%)	TRD (%)	MST (month)	5-YS (%)
Westeel et al. (1998)[28]	PAVE × 3, PE × 1 20/5, 30/10, 40/15	25	Median 72	28	92	Thrombocytopenia*(9) Infection (18) Esophagitis*(9)	3	16	24
Murray et al. (1998)[29]	CAV × 1, PE × 1 20/5, 30/10	55	67	45	89	Infection(4)	5	13	18
Jeremic et al. (1998)[30]	Carbo + oral E × 2 45/30 (twice daily)	72	100	17	75	Leukopenia (8) Thrombocytopenia (12) Infection (3) Esophagitis (3)	NA	15	13

CAV, cyclophosphamide, doxorubicin and vincristine; Carbo, carboplatin; E, etoposide; MST, median survival time; NA, not available; PAVE, cisplatin, doxorubicin, vincristine and etoposide; PE, cisplatin and etoposide; PS, performance status; RR, response rate; TRD, treatment-related death; 5-YS, five-year survival rate.

*Grade 4 only.

acceptable toxicity in elderly patients. Carboplatin is especially useful for the elderly, because it requires only minimum hydration, its non-hematological toxicity is mild, and the dose can be adjusted according to patient's creatinine clearance. Japanese Clinical Oncology Group (JCOG) evaluated toxicity and efficacy of this method in a phase II study (JCOG9409), and showed that grade 4 neutropenia and thrombocytopenia were noted in 44% and 12% of patients, respectively, and that CR and PR were obtained in 6% and 69%, respectively.[25] We started a large phase III trial in 1997, comparing etoposide (80 mg/m^2 days 1–3) and carboplatin (AUC = 5) with etoposide (the same dose) and cisplatin (25 mg/m^2 days 1–3) in elderly patients with SCLC (JCOG 9702). Up to the present, more than 200 patients were registered in this study.

A recent phase III trial showed that a combination of cisplatin and irinotecan was superior to a combination of cisplatin and etoposide in patients with extensive SCLC, but only patients 70 years of age or younger were included in this study.[31] In addition, there is no clinical trial of irinotecan in elderly patients with SCLC. Another anticancer agent promising in the treatment of SCLC is amrubicin, which yielded a response rate of 79% and median survival time of 11 months in patients with extensive SCLC.[32] Further studies are necessary to evaluate these new agents in the treatment of elderly patients with SCLC.

The chemoradiotherapy used in younger patients may be too intensive for most elderly patients with limited SCLC. One approach that avoids excessive toxicity is to reduce the dose of the chemotherapy or radiotherapy. A recent meta-analysis of chemotherapy alone versus chemotherapy plus radiotherapy in patients with limited SCLC demonstrated survival benefit of radiotherapy added to chemotherapy in patients less than 70 years of age, but the benefit disappeared in the older patients.[33] This finding indicates that the standard treatment in this setting might be chemotherapy alone. The currently available phase II studies of treatment of limited SCLC in the elderly, however, showed that two cycles of chemotherapy plus full-dose radiotherapy produced long-term survivors with acceptable toxicity.[28–30] Thus, which modality should be modified remains controversial, but reduced cycles of chemotherapy combined with full-dose radiotherapy appears to be the treatment of choice at present.

The criteria for the classification of elderly patients into two groups in this review were based on PS, function of major organs, and comorbidity. However, they may be inadequate to evaluate this heterogeneous elderly population. In future clinical trials, it will be important to evaluate the influence of cancer treatment on the functional status of the elderly. A comprehensive geriatric assessment designed to improve the health care of elderly people consists mainly of instruments for evaluating activities of daily living, physical function, cognitive function, and emotional status.[34, 35] It has been used as a diagnostic tool to screen for problems and to determine the needs of the geriatric population for in-home assistance, home-health service, or hospital care, but it may be also useful for our purpose.

In conclusion, although the evidence levels based on clinical trials currently available are low, it is possible to select the optimal treatment for elderly patients with SCLC by dividing them into patients in good and poor general condition.

References

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. *Int J Cancer* 1993;54:594–606.
2. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin* 2000;50:7–33.
3. Murren J, Glatstein E, Pass HI. Small cell lung cancer. In: DeVita Jr VT, Hellman S, Rosenberg SA, editors. *Cancer: principles and practice of oncology*. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2001. p. 983–1018.
4. Stephens RJ, Johnson DH. Treatment and outcomes for elderly patients with small cell lung cancer. *Drugs Aging* 2000;17:229–47.
5. Shepherd FA, Bezjak A. Treatment of small cell lung cancer in the elderly patients. In: Pass HI, Mitchell JB, Johnson DH, Turrisi AT, Minna JD, editors. *Lung cancer: principles and practice*. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 1081–91.
6. Sekine I, Fukuda H, Kunitoh H, Saijo N. Cancer chemotherapy in the elderly. *Jpn J Clin Oncol* 1998;28:463–73.
7. American Society of Clinical Oncology. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. *J Clin Oncol* 1997;15:2996–3018.
8. Nou E. Full chemotherapy in elderly patients with small cell bronchial carcinoma. *Acta Oncol* 1996;35:399–406.
9. Dajczman E, Fu LY, Small D, Wolkove N, Kreisman H. Treatment of small cell lung carcinoma in the elderly. *Cancer* 1996;77:2032–8.
10. Tebbutt NC, Snyder RD, Burns WI. An analysis of the outcomes of treatment of small cell lung cancer in the elderly. *Aust N Z J Med* 1997;27:160–4.
11. Jara C, Gomez-Aldaravi JL, Tirado R, et al. Small-cell lung cancer in the elderly – is age of patient a relevant factor? *Acta Oncol* 1999;38:781–6.
12. Oshita F, Kurata T, Kasai T, et al. Prospective evaluation of the feasibility of cisplatin-based chemotherapy for elderly lung cancer patients with normal organ functions. *Jpn J Cancer Res* 1995;86:1198–202.
13. Goodwin JS, Hunt WC, Humble CG, Key CR, Samet JM. Cancer treatment protocols. Who gets chosen? *Arch Intern Med* 1988;148:2258–60.

14. Paccagnella A, Favaretto A, Cipiani A, et al. Treatment of small cell lung cancer in elderly patients. *Proc Am Soc Clin Oncol* 1996;15:387 (abstract).
15. Siu LL, Shepherd FA, Murray N, et al. Influence of age on the treatment of limited-stage small-cell lung cancer. *J Clin Oncol* 1996;14:821–8.
16. Yuen AR, Zou G, Turrisi AT, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer* 2000;89: 1953–60.
17. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. *Lancet* 1996; 348:563–6.
18. Souhami RL, Spiro SG, Rudd RM, et al. Five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. *J Natl Cancer Inst* 1997;89:577–80.
19. Medical Research Council Lung Cancer Working Party. Randomised trial of four-drug vs less intensive two-drug chemotherapy in the palliative treatment of patients with small-cell lung cancer (SCLC) and poor prognosis. Medical Research Council Lung Cancer Working Party. *Br J Cancer* 1996;73:406–13.
20. James LE, Gower NH, Rudd RM, et al. A randomised trial of low-dose/high-frequency chemotherapy as palliative treatment of poor-prognosis small-cell lung cancer: a Cancer Research Campaign trial. *Br J Cancer* 1996;73: 1563–8.
21. Earl HM, Rudd RM, Spiro SG, et al. A randomised trial of planned versus as required chemotherapy in small cell lung cancer: a Cancer Research Campaign trial. *Br J Cancer* 1991; 64:566–72.
22. Evans WK, Radwi A, Tomiak E, et al. Oral etoposide and carboplatin. Effective therapy for elderly patients with small cell lung cancer. *Am J Clin Oncol* 1995;18:149–55.
23. Matsui K, Masuda N, Fukuoka M, et al. Phase II trial of carboplatin plus oral etoposide for elderly patients with small-cell lung cancer. *Br J Cancer* 1998;77:1961–5.
24. Westeel V, Murray N, Gelmon K, et al. New combination of the old drugs for elderly patients with small-cell lung cancer: a phase II study of the PAVE regimen. *J Clin Oncol* 1998;16:1940–7.
25. Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. *J Clin Oncol* 1999;17:3540–5.
26. Samantas E, Skarlos DV, Pectasides D, et al. Combination chemotherapy with low doses of weekly carboplatin and oral etoposide in poor risk small cell lung cancer. *Lung Cancer* 1999;23:159–68.
27. Pignon T, Gregor A, Schaake Koning C, et al. Age has no impact on acute and late toxicity of curative thoracic radiotherapy. *Radiother Oncol* 1998;46: 239–48.
28. Westeel V, Murray N, Gelmon K, et al. New combination of the old drugs for elderly patients with small-cell lung cancer: a phase II study of the PAVE regimen. *J Clin Oncol* 1998;16:1940–7.
29. Murray N, Grafton C, Shah A, et al. Abbreviated treatment for elderly, infirm, or noncompliant patients with limited-stage small-cell lung cancer. *J Clin Oncol* 1998;16:3323–8.
30. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Carboplatin, etoposide, and accelerated hyperfractionated radiotherapy for elderly patients with limited small cell lung carcinoma: a phase II study. *Cancer* 1998;82:836–41.
31. Noda K, Nishiwaki Y, Kawahara M, et al. Japan Clinical Oncology Group. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85–91.
32. Yana T, Negoro S, Yokota M, Fukkuoka M. Phase II study of amrubicin (SM-5887), a 9-amino-anthracycline, in previously untreated patients with extensive stage small-cell lung cancer: a West Japan Lung Cancer Group Trial. *Proc Am Soc Clin Oncol* 1998;17:450a.
33. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618–24.
34. Applegate WB, Blass JP, Williams TF. Instruments for the functional assessment of older patients. *N Engl J Med* 1990; 322:1207–14.
35. Stuch AE, Siu AL, Wieland GD, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 1993;342:1032–6.

Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

Ikuo Sekine,[1] Kazumasa Noda,[3] Fumihiro Oshita,[3] Kouzou Yamada,[3] Manabu Tanaka,[3] Kosuke Yamashita,[4] Hiroshi Nokihara,[1] Noboru Yamamoto,[1] Hideo Kunitoh,[1] Yuichiro Ohe,[1] Tomohide Tamura,[1] Tetsuro Kodama,[1] Minako Sumi[2] and Nagahiro Saijo[1]

Divisions of [1]Thoracic Oncology and Internal Medicine and [2]Radiotherapy, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045; and Divisions of [3]Thoracic Oncology and [4]Radiation Oncology, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815

(Received April 28, 2004/Revised June 23, 2004/Accepted June 25, 2004)

To determine the recommended phase II dose of vinorelbine in combination with cisplatin and thoracic radiotherapy (TRT) in patients with unresectable stage III non-small cell lung cancer (NSCLC), 18 patients received cisplatin (80 mg/m²) on day 1 and vinorelbine (20 mg/m² in level 1, and 25 mg/m² in level 2) on days 1 and 8 every 4 weeks for 4 cycles. TRT consisted of a single dose of 2 Gy once daily for 3 weeks followed by a rest of 4 days, and then the same TRT for 3 weeks to a total dose of 60 Gy. Fifteen (83%) patients received 60 Gy of TRT and 14 (78%) patients received 4 cycles of chemotherapy. Ten (77%) of 13 patients at level 1 and all 5 patients at level 2 developed grade 3–4 neutropenia. Four (31%) patients at level 1 and 3 (60%) patients at level 2 developed grade 3–4 infection. None developed ≥grade 3 esophagitis or lung toxicity. Dose-limiting toxicity was noted in 33% of the patients in level 1 and in 60% of the patients in level 2. The overall response rate (95% confidence interval) was 83% (59–96%) with 15 partial responses. The median survival time was 30.4 months, and the 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively. In conclusion, the recommended dose is the level 1 dose, and this regimen is feasible and promising in patients with stage III NSCLC. (Cancer Sci 2004; 95: 691–695)

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for about 25% of all lung cancer cases.[1] Successful treatment of this disease rests on the control of both clinically apparent intrathoracic disease and occult systemic micrometastases, and therefore a combination of systemic chemotherapy and thoracic radiotherapy is indicated in many patients with good performance status and no pleural effusion.[2] Concurrent chemoradiotherapy is superior to the sequential approach, as shown by recent phase III trials in unresectable stage III NSCLC, in which the median survival time was 15.0 to 17.0 months in the concurrent arm and 13.3 to 14.6 months in the sequential arm, although acute esophagitis was more severe in the concurrent arm.[3–5] Chemotherapy regimens combined with simultaneous thoracic radiotherapy have consisted of cisplatin plus etoposide and cisplatin plus vinca alkaloids,[3,4] and a combination of cisplatin plus vindesine, with or without mitomycin, has been widely used in Japan.[5–8]

Vinorelbine, a new semisynthetic vinca alkaloid with a substitution in the catharanthine ring, interacts with tubulin and microtubule-associated proteins in a manner different from the older vinca alkaloids, and it more selectively depolymerizes microtubules in mitotic spindles.[9] Several randomized trials have shown vinorelbine to be more active against advanced or metastatic NSCLC than vindesine as a single agent or in combination with cisplatin.[10–13] Thus, incorporation of vinorelbine into concurrent chemoradiotherapy instead of vindesine is an important strategy for the treatment of locally advanced NSCLC. The objective of this study was to determine the maximum tolerated dose (MTD) and recommended dose of vinorelbine for phase II studies in combination with cisplatin, with or without mitomycin, and thoracic radiotherapy for patients with unresectable stage III NSCLC. We planned to start with the cisplatin and vinorelbine combination and then add mitomycin.

Patients and Methods

Patient selection. The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1[14]; adequate bone marrow function (12.0×10^9/liter ≥white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase ≤twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml/min); and a PaO_2 of 70 Torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment evaluation. The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment schedule. The dose levels and doses of each anticancer agent are shown in Table 1. Cisplatin and vinorelbine were administered at dose levels 1 and 2. It was planned to give cisplatin, vinorelbine, and mitomycin at dose levels 3–5, but because the MTD was determined to be dose level 2, dose levels 3–5 were not used. Cisplatin was administered on day 1 by intravenous infusion over 60 min together with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 40 ml of normal saline was administered by bolus intravenous injection on days 1 and 8. All patients received prophylactic antiemetic ther-

E-mail: isekine@ncc.go.jp

apy consisting of a 5HT3-antagonist and a steroid. This chemotherapy regimen was repeated every 4 weeks for 4 cycles.

Thoracic radiotherapy with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV at a single dose of 2 Gy once daily given 15 times over 3 weeks was begun on day 2 of the first cycle of cisplatin and vinorelbine chemotherapy, and followed by a short rest period of 4 days. The same radiotherapy was begun on day 1 of the second cycle of chemotherapy to a total dose of 60 Gy. The clinical target volume (CTV) was based on conventional chest X-ray and CT scans, and included the primary lesion (CTV1), involved lymph nodes whose short diameter was 1 cm or larger (CTV2), and the ipsilateral pulmonary hilum and bilateral mediastinum area (CTV3). Anterior and posterior parallel opposed fields encompassed the initial planned target volume (PTV), consisting of CTV1–3 with the superior and inferior field margins extended to 1 to 2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The boost PTV included only CTV1–2 based on the second CT scans with the same margins. The spinal cord dose was limited to 40 Gy by using oblique parallel opposed fields.

Toxicity assessment and treatment modification. Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria version 2.0 issued in 1998, and late toxicity associated with thoracic radiotherapy was graded according to the RTOG Late Radiation Morbidity Scoring Schema.[15] Vinorelbine administration on day 8 was omitted if any of the following toxicities was noted: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. The doses of cisplatin and vinorelbine were reduced by 25% in all subsequent cycles if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, or grade 3 or severer non-hematological toxicity, except for nausea and vomiting. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, esophagitis ≥grade 3, fever ≥38°C, performance status ≥3, or PaO_2 <70 Torr. Thoracic radiotherapy was terminated if this toxicity persisted for more than 2 weeks. Granulocyte colony-stimulating factor support was used if the neutrophil count was $<0.5\times10^9$/liter for more than 4 days, the WBC count was $<1.0\times10^9$/liter, or febrile neutropenia ≥grade 3 was noted.

Dose-limiting toxicity, MTD, and recommended dose for phase II studies. The dose-limiting toxicity (DLT) was defined as a neutrophil count $<0.5\times10^9$/liter lasting 4 days or longer, febrile neutropenia ≥grade 3, platelet count $<20\times10^9$/liter, grade 3 or more severe non-hematological toxicity other than nausea and vomiting, and patient's refusal to receive subsequent treatment. Doses were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If one or none of them experienced DLT, the next cohort of patients was treated at the next higher dose level. If 2 of the 6 patients experienced DLT, then 6 additional patients were enrolled at the same dose level to make a total of 12 patients. If 4 or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. If 3 of the initial 6 patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Response evaluation. Objective tumor response was evaluated according to the WHO criteria issued in 1979.[16] A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks with no new lesions appearing. A partial response (PR) was defined as an at least 50% decrease in total tumor size for at least 4 weeks without the appearance of new lesions. No change (NC) was defined as the absence of a partial or complete response with no progressive or new lesions observed for at least 4 weeks. Progressive disease was defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions.

Study design, data management, and statistical considerations. This study was designed as a phase I study at two institutions, the National Cancer Center Hospital and Kanagawa Cancer Center. The protocol and consent form were approved by the Institutional Review Board of each institution. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 18 months were planned. Overall survival time and progression-free survival time were estimated by the Kaplan-Meier method.[17] Survival time was measured from the date of registration to the date of death due to any cause. Progression-free survival time was measured from the date of registration to the date of disease progression or death. Patients who were lost to follow-up without event were censored at the date of their last known follow-up.

Table 1. Dose level and the dose of each anticancer agent

Dose level	Cisplatin (mg/m²)	Vinorelbine (mg/m²)	Mitomycin (mg/m²)
−1	80	15	—
1	80	20	—
2	80	25	—
3	80	15	8
4	80	20	8
5	80	25	8

Results

Registration and characteristics of the patients. From October 1999 to August 2000, 13 patients were registered at dose level 1 and 5 patients at dose level 2. The detailed demographic characteristics of the patients are listed in Table 2. All patients had unresectable IIIA-N2 or IIIB disease. One of the 6 patients enrolled at dose level 1 developed bacterial meningitis during the second cycle of chemotherapy, and that case is described in detail elsewhere.[18] We did not include it in the assessment of DLT, because the bacterial meningitis was not specifically related to treatment. We registered another patient at the same dose level, and 2 cases of DLT were noted among the initial 6 patients evaluable for DLT. We added another 6 patients, and DLT was noted in 4 of the 12 patients registered at the dose level 1. Of the 5 patients registered at level 2, 3 patients developed DLT. This dose level was determined to be the MTD, and patient accrual to this study was terminated.

Treatment delivery. Treatment delivery was generally well maintained, and it did not differ between the two dose levels (Table 3). Full dose (60 Gy) thoracic radiotherapy was completed in 77% and 100% of the patients at dose levels 1 and 2,

Table 2. Patients' characteristics

		Median (range)	N (%)
Number of patients			18
Gender	male		16 (89)
	female		2 (11)
Age	median (range)	59 (48–69)	
PS	0		4 (22)
	1		14 (78)
Body weight loss	<5%		12 (67)
	5–9%		4 (22)
	≥10%		2 (11)
T-factor	1		1 (6)
	2		6 (33)
	3		7 (39)
	4		4 (22)
N-factor	2		11 (61)
	3		7 (39)
Clinical stage	IIIA		9 (50)
	IIIB		9 (50)
Histology	adenocarcinoma		14 (78)
	squamous cell carcinoma		3 (17)
	adenosquamous carcinoma		1 (6)

Table 3. Treatment delivery

	Dose level 1 (N=13)	Dose level 2 (N=5)
	N (%)	N (%)
Initial irradiation field (cm^2) median (range)	171 (128–529)	182 (128–248)
Total dose of radiotherapy (Gy)		
60	10 (77)	5 (100)
50–59	1 (8)	0
<50	2 (15)	0
Delay of radiotherapy (days)[1]		
<5	6 (60)	3 (60)
5≤	4 (40)	2 (40)
Number of chemotherapy cycles		
4	10 (77)	4 (80)
3	0	1 (20)
2	2 (15)	0
1	1 (8)	0
Omission of vinorelbine administration on day 8		
0	9 (69)	2 (40)
1	4 (31)	2 (40)
3	0	1 (20)

1) Evaluated in patients who received 60 Gy radiotherapy (N=15).

respectively. Delays in radiotherapy evaluated in patients who completed the full course of radiotherapy amounted to less than 5 days in 60% of the patients at both levels. Full cycles (4 cycles) of chemotherapy were administered to 77% and 80% of the patients at dose levels 1 and 2, respectively, but vinorelbine administration on day 8 was more frequently omitted at dose level 2 (Table 3).

Toxicity, MTD, and the recommended dose for phase II trials. Acute severe toxicity was mainly hematological (Table 4). Grade 3–4 leukopenia and neutropenia were noted in 77% and 100% of the patients at dose levels 1 and 2, respectively. Grade 3 anemia was observed in 23% and 20% of the patients at dose levels 1 and 2, respectively, but no blood transfusions were required. Thrombocytopenia was mild. Grade 4 transaminase elevation was observed in 1 patient during the first cycle of chemotherapy, but no subjective manifestations associated with liver dysfunction were noted. Chemotherapy was discontinued and the transaminases quickly decreased to within their normal ranges. Transient asymptomatic grade 3 hyponatremia was noted in 1 patient. Grade 3–4 infection was noted in 7 patients. Bacterial meningitis unassociated with neutropenia developed on day 6 of the second cycle of chemotherapy in 1 patient.[18] The other grade 3–4 infections were all associated with neutropenia. Esophagitis was mild in this study, and no grade 3–4 esophagitis was noted. No deaths occurred during or within 30 days of therapy.

DLT was noted in 4 of the 12 (33%) evaluable patients at dose level 1, and in 3 of the 5 (60%) at dose level 2. Six of these 7 DLTs were grade 3–4 infection associated with neutropenia, and the other 1 was grade 4 transaminase elevation. Thus, we determined that dose level 2 was the MTD, and dose level 1 was recommended as the dose for phase II trials.

Table 4. Acute toxicity

Toxicity	Dose level 1 (*N*=13), Grade					Dose level 2 (*N*=5), Grade				
	1	2	3	4	3–4 (%)	1	2	3	4	3–4 (%)
Hematological										
Leukopenia	0	2	9	1	(77)	0	0	4	1	(100)
Neutropenia	1	1	7	3	(77)	0	0	1	4	(100)
Anemia	4	6	3	0	(23)	2	2	1	0	(20)
Thrombocytopenia	1	2	0	0	(0)	1	0	0	0	(0)
Non-hematological										
AST	2	0	0	1	(8)	1	0	0	0	(0)
ALT	7	0	0	1	(8)	0	1	0	0	(0)
Total bilirubin	2	1	0	0	(0)	2	0	0	0	(0)
Creatinine	2	2	0	0	(0)	1	0	0	0	(0)
Hyponatremia	6	0	1	0	(8)	1	0	0	0	(0)
Infection	1	3	2	2	(31)	0	0	3	0	(60)
Nausea	4	1	0	0	(0)	3	0	0	0	(0)
Diarrhea	0	1	0	0	(0)	0	0	0	0	(0)
Stomatitis	2	0	0	0	(0)	0	2	0	0	(0)
Esophagitis	6	1	0	0	(0)	4	0	0	0	(0)
Sensory neuropathy	2	0	0	0	(0)	0	0	0	0	(0)

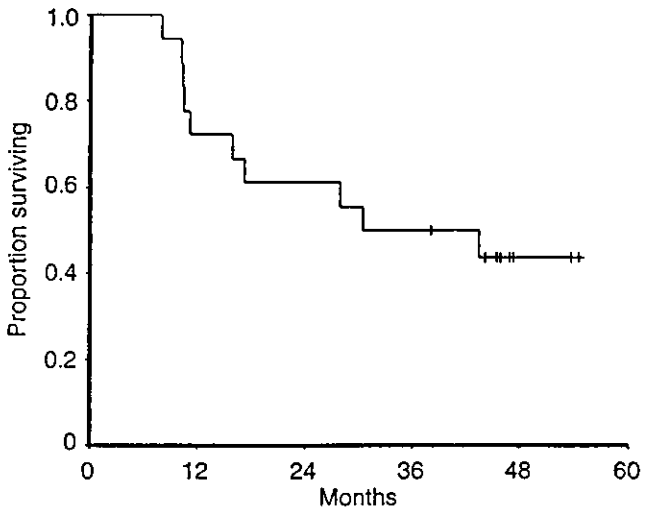

Fig. 1. Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

Late lung toxicity associated with thoracic radiotherapy was grade 3 in 1 (6%) patient, grade 2 in 4 (22%) patients, and grade 1 in 8 (44%) patients. No late esophageal toxicity was noted.

Objective responses, relapse pattern, and survival. All patients were included in the analyses of tumor response and survival. No CR, 15 PRs, and 1 NC were noted, and the overall response rate (95% confidence interval) was 83% (59–96%). Relapse was noted in 12 (67%) of 18 patients. Initial relapse sites were locoregional alone in 5 (28%) patients, locoregional and distant in 3 (17%) patients, and distant alone in 4 (22%) patients. Brain metastasis was detected in 5 patients, and the brain was the most frequent site of distant metastasis. The median progression-free survival time was 15.6 months, and the median overall survival time was 30.4 months. The 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively (Fig. 1).

Discussion

The combination of cisplatin, vindesine, and mitomycin with concurrent thoracic radiotherapy has been shown to yield an encouraging survival outcome, a median survival time of 17–19 months, and a 5-year survival rate of 16% in patients with unresectable stage III NSCLC.[5,7,8] A Japanese randomized trial revealed that replacement of vindesine by vinorelbine in combination with cisplatin and mitomycin yielded a promising response rate (57% versus 38%, $P=0.025$) and median survival time (15 months versus 11 months, $P<0.01$) in patients with stage IIIB or IV NSCLC.[13] Thus, the combination of cisplatin, vinorelbine, and mitomycin is a chemotherapy regimen with potential for combination with concurrent thoracic radiotherapy. The present study, however, showed that a DLT developed in 60% of patients who received cisplatin and vinorelbine 25 mg/m^2 days 1 and 8 (level 2), and since the DLTs were associated with myelosuppression, which is the major critical toxicity of mitomycin, we concluded that it would be impossible to incorporate mitomycin into this regimen.

The recommended doses of vinorelbine of 20 mg/m^2 on days 1 and 8 and cisplatin of 80 mg/m^2 on day 1 repeated every 4 weeks in this study are comparable to the doses used in the CALGB (vinorelbine 15 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 repeated every 3 weeks),[19,20] and the Czech Lung Cancer Cooperative Group (vinorelbine 12.5 mg/m^2 on days 1, 8, and 15 and cisplatin 80 mg/m^2 on day 1, repeated every 4 weeks),[21] but lower than in a Mexican study (vinorelbine at 25 mg/m^2 on days 1 and 8 and cisplatin 100 mg/m^2 on day 1, repeated every 3 weeks).[22] These recommended doses are also lower than expected when compared with the recommended vinorelbine dose combined with cisplatin for metastatic NSCLC (vinorelbine 30 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1, repeated every 3 weeks),[23] and when compared with the results of vindesine, cisplatin, and mitomycin combined with thoracic radiotherapy, where the full doses can be administered concurrently.[8] Thus, vinorelbine can be safely administered with cisplatin and concurrent thoracic radiotherapy at a maximum dose of two-thirds the optimal dose without radiotherapy.

The results for response and survival in this study, however, were very encouraging. This may have been attributable to patient selection bias, but the percentage of patients who had stage IIIB disease in this study was similar to the percentage in the CALGB randomized phase II study.[20] In addition, 33% of the patients in this study had ≥5% body weight loss, whereas only 7% of the patients did in that study.[20] The median survival time was 30.4 months and exceeded the results of concurrent

chemoradiotherapy with old drug combinations that yielded a median survival time of 15–19 months.[3-8] Thus, it could be argued that the combination of cisplatin and vinorelbine is more active for locally advanced NSCLC than the older drug combinations, although there have not been any randomized trials comparing this regimen with old drug combinations in combination with thoracic radiotherapy in patients with stage III NSCLC. Our results also seem better than those of other trials using concurrent cisplatin, vinorelbine, and thoracic radiotherapy, in which the median survival time was 13 to 18 months.[20,22] Those trials used induction chemotherapy followed by chemoradiotherapy. Since the response rate to induction chemotherapy is no more than 40%, induction chemotherapy may be disadvantageous. This issue is being evaluated in an on-going CALGB phase III trial.

Severe esophagitis and pneumonitis have been DLTs in many trials of concurrent chemoradiotherapy, but neither was observed in this study. Nevertheless, since the occurrence of these non-hematological toxicities associated with thoracic radiotherapy is sporadic, the sample size in this study may have been too small to detect them. Thus, careful observation for these toxicities is needed in further phase II and phase III trials to definitely establish the safety profile of this regimen.

In conclusion, cisplatin and vinorelbine chemotherapy combined with concurrent full-dose thoracic radiotherapy is feasible, and the recommended dose of vinorelbine for phase II trials is 20 mg/m^2 on days 1 and 8 repeated every 4 weeks. This regimen was highly active in patients with stage III NSCLC.

This work was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan, and was presented in part at the 42th Annual Meeting of the Japan Lung Cancer Society, Osaka, Japan, November 1–2, 2001. We thank Ms. Yuko Yabe for preparation of the manuscript.

1. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997; **111**: 1710–7.
2. Jett JR, Scott WJ, Rivera MP, Sause WT and American College of Chest Physicians. Guidelines on treatment of stage IIIB non-small cell lung cancer. *Chest* 2003; **123**: 221S–5S.
3. Pierre F, Maurice P, Gilles R, Pascal T, Pierre-Jean S, Hervé L, Alain V, Jean-Yves D, Francoise M, Fancoise M. A randomized phase III trial of sequential chemoradiotherapy in locally advanced non-small-cell lung cancer. *Proc Am Soc Clin Oncol* 2001; **20**: 312a (abstr 1246).
4. Curren W Jr, Scott C, Langer C, Komaki R, Lee J, Hauser S, Movsas B, Wasserman TH, Rosenthal S, Byhardt R, Sause W, Cox J. Phase III comparison of sequential vs concurrent chemoradiation for patients with unresectable stage III non-small-cell lung cancer (NSCLC): initial report of the Radiation Therapy Oncology Group (RTOG) 9410. *Proc Am Soc Clin Oncol* 2000; **19**: 484a (abstr 1891).
5. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Katagami N, Ariyoshi Y. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999; **17**: 2692–9.
6. Kubota K, Tamura T, Fukuoka M, Furuse K, Ikegami H, Ariyoshi Y, Kurita Y, Saijo N. Phase II study of concurrent chemotherapy and radiotherapy for unresectable stage III non-small-cell lung cancer: long-term follow-up results. Japan Clinical Oncology Group Protocol 8902. *Ann Oncol* 2000; **11**: 445–50.
7. Furuse K, Kubota K, Kawahara M, Kodama N, Ogawara M, Akira M, Nakajima S, Takada M, Kusunoki Y, Negoro S, Matsui K, Masuda N, Takifuji N, Kudoh S, Nishioka M, Fukuoka M. Phase II study of concurrent radiotherapy and chemotherapy for unresectable stage III non-small-cell lung cancer. Southern Osaka Lung Cancer Study Group. *J Clin Oncol* 1995; **3**: 869–75.
8. Atagi S, Kawahara M, Hosoe S, Ogawara M, Kawaguchi T, Okishio K, Naka N, Sunami T, Mitsuoka S, Akira M. A phase II study of continuous concurrent thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non-small cell lung cancer. *Lung Cancer* 2002; **36**: 105–11.
9. Sekine I, Saijo N. Novel combination chemotherapy in the treatment of non-small cell lung cancer. *Exp Opin Pharmacother* 2000; **1**: 1131–61.
10. Furuse K, Fukuoka M, Kuba M, Yamori S, Nakai Y, Negoro S, Katagami N, Takada Y, Kinuwaki E, Kawahara M, Kubota K, Sakuma A, Niitani H. Randomized study of vinorelbine (VRB) versus vindesine (VDS) in previously untreated stage IIIB or IV non-small-cell lung cancer (NSCLC). The Japan Vinorelbine Lung Cancer Cooperative Study Group. *Ann Oncol* 1996; **7**: 815–20.
11. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, Riviere A, Lianes P, Chomy P, Cigolari S, Gottfried M, Ruffie P, Panizo A, Gaspard MH, Ravaioli A, Besenval M, Besson F, Martinez A, Berthaud P, Tursz T. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994; **12**: 360–7.
12. Perol M, Guerin JC, Thomas P, Poirier R, Carles P, Robinet G, Kleisbauer JP, Paillotin D, Vergnenegre A, Balmes P, Touron D, Grivaux M, Pham E. Multicenter randomized trial comparing cisplatin-mitomycin-vinorelbine versus cisplatin-mitomycin-vindesine in advanced non-small cell lung cancer. 'Groupe Francais de Pneumo-Cancerologie.' *Lung Cancer* 1996; **14**: 119–34.
13. Kawahara M, Furuse K, Nishiwaki Y, Horai T, Saijo N, Hasegawa K, Ohashi Y, Niitani H. Randomized study of vinorelbine (VRB) or vindesine (VDS) with cisplatin (C) and mitomycin (M) as induction chemotherapy in stage IIIB or IV non-small cell lung cancer (NSCLC)-final results. *Proc Am Soc Clin Oncol* 2000; **19**: 489a (abstr 1914).
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbonne PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55.
15. JCOG Administrational Committee: National Cancer Institute-Common Toxicity Criteria (NCI-CTC Version 2.0, Jan 30, 1998). Japanese edition by JCOG. Available at http://www.med.gunma-u.ac.jp/event/CTCJ_v20.pdf
16. WHO. Handbook for reporting results of cancer treatment. WHO Offset Publication no. 48. Geneva: World Health Organization; 1979.
17. Armitage P, Berry G. Survival analysis. In: Statistical methods in medical research. 3rd ed. Oxford: Blackwell Sci Publ; 1994. p. 469–92.
18. Sekine I, Matsuda T, Saisho T, Watanabe H, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Kodama T, Saijo N. Bacterial meningitis observed in a phase I trial of vinorelbine, cisplatin and thoracic radiotherapy for non-small cell lung cancer: report of a case and discussion on dose-limiting toxicity. *Jpn J Clin Oncol* 2000; **30**: 401–5.
19. Masters GA, Haraf DJ, Hoffman PC, Drinkard LC, Krauss SA, Ferguson MK, Olak J, Samuels BL, Golomb HM, Vokes EE. Phase I study of vinorelbine, cisplatin, and concomitant thoracic radiation in the treatment of advanced chest malignancies. *J Clin Oncol* 1998; **16**: 2157–63.
20. Vokes EE, Herndon JE 2nd, Crawford J, Leopold KA, Perry MC, Mikker AA, Green MR. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002; **20**: 4191–8.
21. Zatloukal P, Petruzelka L, Zemanova M, Krejbich F, Havel L. Vinorelbine (VRL) plus cisplatin (CDDP) and concurrent radiotherapy in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1998; **17**: 505a (abstr 1947).
22. Alcedo J, Gallardo D, Lopez-Mariscal A, Calderillo G, Green L, Correa E, Zamora J, Mohar A. Cisplatin/vinorelbine (CDDP/VNR) and radiotherapy (XRT) in advanced non-small cell lung cancer (ANSCLC): an effective and feasible option with no need for dose reduction. *Proc Am Soc Clin Oncol* 1999; **18**: 494a (abstr 1905).
23. Hotta K, Sekine I, Tamura T, Sawada M, Watanabe H, Kusaba H, Akiyama Y, Inoue A, Shimoyama T, Nokihara H, Ueda Y, Yamamoto N, Kunitoh H, Ohe Y, Kodama T, Saijo N. A phase I/II study of cisplatin and vinorelbine chemotherapy in patients with advanced non-small cell lung cancer. *Jpn J Clin Oncol* 2001; **31**: 596–600.

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

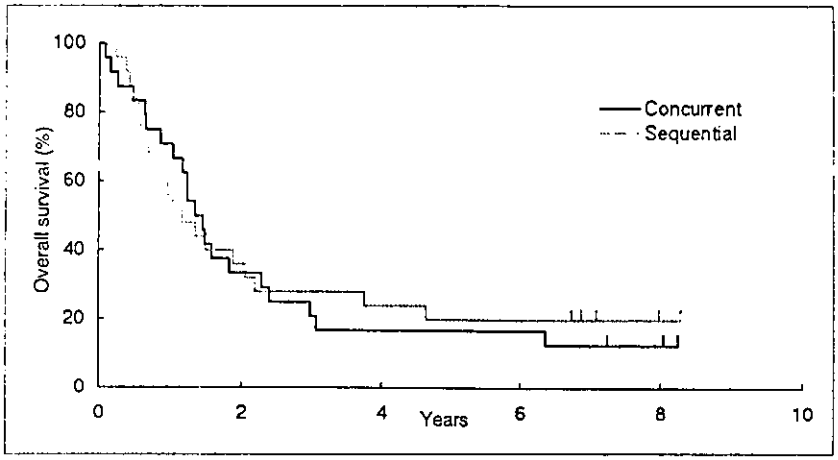

Fig. 1. Overall survival in patients according to treatment.

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

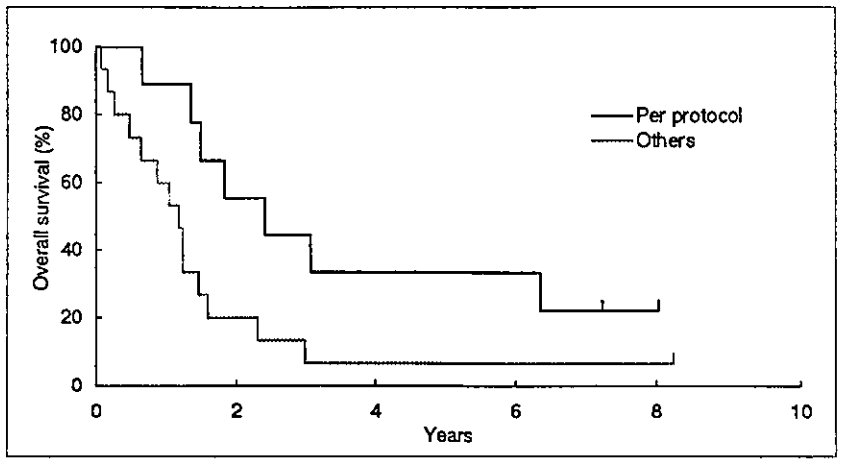

Fig. 2. Overall survival in per-protocol patients and others. Others were patients with interruption or with incomplete radiation therapy.

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.

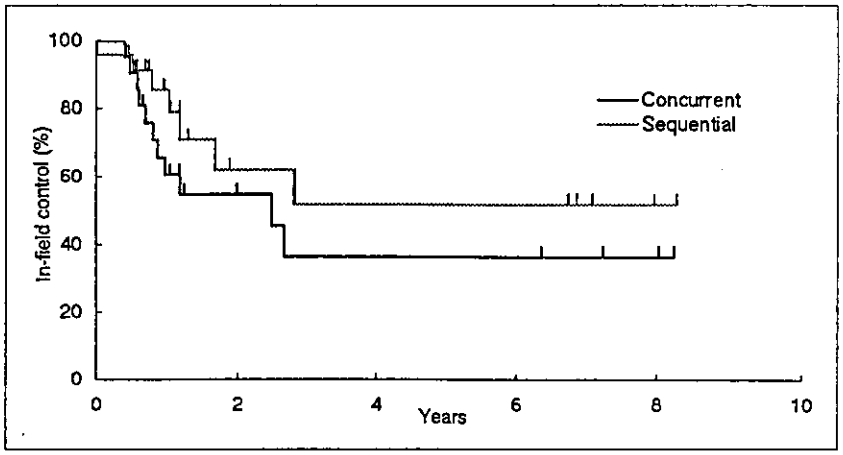

Fig. 3. In-field control in patients who received the full dose of radiation therapy.

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) 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

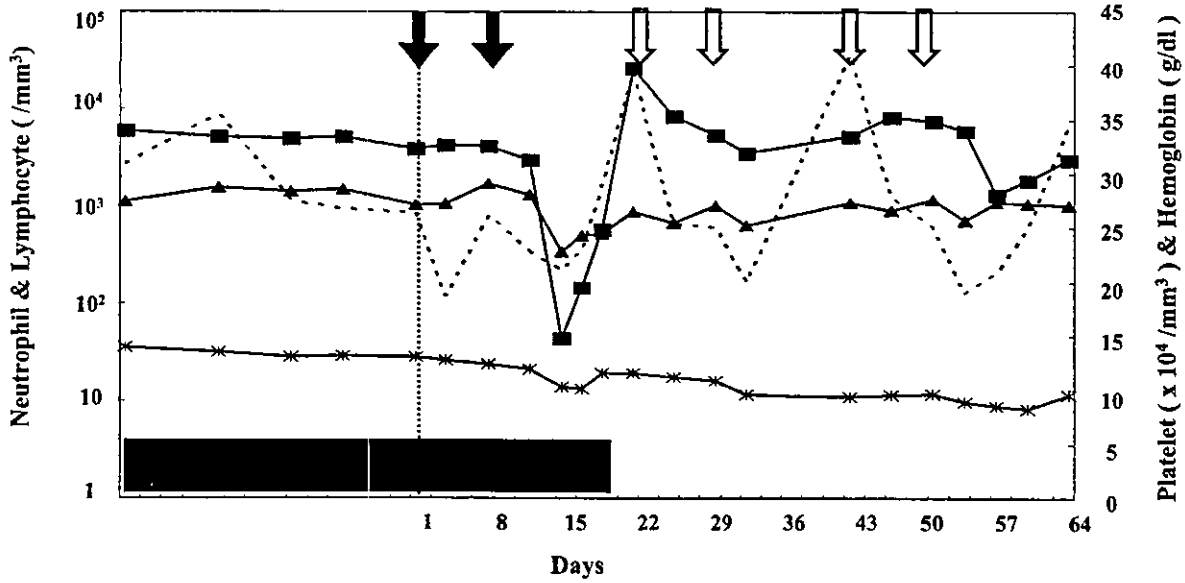

Fig. 1 Clinical course and hematocyte counts of Case 2 (74-year-old female): (▬) gefitinib 250 mg per day oral administration; (➡) intravenous vinorelbine 25 mg/m^2; (⇒) intravenous vinorelbine 20 mg/m^2; (■) neutrophil count; (▲) lymphocyte count; (···) platelet count; (✳) hemoglobin value.

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

Lung Cancer (2004) 43, 167–173

ELSEVIER

LUNG CANCER

www.elsevier.com/locate/lungcan

A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304)

Hirohito Tada[a,*], Ryosuke Tsuchiya[b,1], Yukito Ichinose[c,2], Teruaki Koike[d,3], Nobuhiro Nishizawa[e,4], Kanji Nagai[f,5], Harubumi Kato[g,6]

Japan Clinical Oncology Group

[a] *Division of General Thoracic Surgery, Osaka City General Hospital, 2-13-22 Miyakojima-Hondori, Miyakojima-ku, Osaka 534-0004, Japan*
[b] *Division of General Thoracic Surgery, National Cancer Center, 5-1-1 Tsukiji, Chuou-ku, Tokyo 104-0045, Japan*
[c] *Division of Pulmonology, National Kyushu Cancer Center, 3-1-1 Notame, Minami ku, Fukuoka 811-1395 Japan*
[d] *Division of General Thoracic Surgery, Niigata Cancer Center, 2-15-3 Kawagishi tyo, Niigata 951-8566 Japan*
[e] *Division of General Thoracic Surgery, Saku General Hospital, 197 Ooaza-usuta, Usuta-tyo, Minami-saku gun, Nagano 384-0301 Japan*
[f] *Division of General Thoracic Surgery, National Cancer Center East, 6-5-1 Kashinoha, Kashiwa, Tiba 277-8577 Japan*
[g] *Department of Surgery, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku Tokyo 160-0023 Japan*

Received 28 April 2003; received in revised form 25 August 2003; accepted 28 August 2003

KEYWORDS
Non-small cell lung cancer;
Adjuvant chemotherapy;
CDDP;
Vindesine;
N2 disease;
Complete resection

Summary The purpose of this study was to evaluate the efficacy of adjuvant chemotherapy with three courses of cisplatin and vindesine, in comparison to observation only, for N2 non-small cell lung cancer that had been completely resected. Patients with pathologically demonstrated mediastinal lymph node metastasis (N2), who had undergone complete resection, were randomized to observation or adjuvant chemotherapy (cisplatin 80 mg/m^2 on day 1; vindesine 3 mg/m^2 on days 1 and 8: ×3 courses). Cycles started within 6 weeks after complete resection and were repeated every 4 weeks. This trial was terminated before accumulation of the planned numbers for registration because of a slow accrual rate. A total of 119 patients were randomized (59 patients in the adjuvant arm and 60 with surgery alone). The median survival

*Corresponding author. Tel.: +81-6-6929-1221; fax: +81-6-6929-1090.
E-mail address: htada@attglobal.net (H. Tada).
[1] Tel.: +81-3-3542-2511; fax: +81-3-3542-2547.
[2] Tel.: +81-92-541-3231; fax: +81-92-551-4585.
[3] Tel.: +81-25-266-5111; fax: +81-25-266-5112.
[4] Tel.: +81-267-82-3131; fax: +81-267-82-9638.
[5] Tel.: +81-4-7133-1111; fax: +81-4-7131-9960.
[6] Tel.: +81-3-3342-6111; fax: +81-3-3349-0326.

0169-5002/$ - see front matter
doi:10.1016/j.lungcan.2003.08.028

was 36 months for both groups. Postoperative cisplatin with vindesine chemotherapy was not shown to be efficacious in cases of completely resected N2 non-small cell lung cancer in this setting of timing, dose and agents studied.

1. Introduction

Even completely resected non-small cell lung cancer (NSCLC) usually relapses with distant metastases. Many adjuvant chemotherapy trials have been conducted to reduce the incidence of postoperative distant metastases. Holmes et al. reported that adjuvant cyclophosphamide, doxorubicin, and cisplatin (CAP) therapy improved disease-free survival for stage II-III adenocarcinomas [1]. Since then, many cisplatin based adjuvant chemotherapy trials have been conducted around the world. Most trials for adjuvant chemotherapy have neither reduced distant metastases nor local recurrence.

Mountain and Dresler reported that some patients with stage I (70-80%) and II (50%) disease can be cured by surgery alone [2]. For these patients, adjuvant chemotherapy would be unnecessary. Postoperative stage IIIA disease relapses in more than two-thirds of cases treated surgically. There are very few stage IIIA patients who could be cured with surgery alone, in whom adjuvant chemotherapy would be unnecessary. The Japanese Clinical Oncology Group (JCOG) conducted a randomized study of postoperative adjuvant chemotherapy focusing only on stage IIIA NSCLC [3], but showed no survival benefit of adjuvant chemotherapy compared with observation alone. There were more cases of N2 disease enrolled in the adjuvant chemotherapy group than in the surgery alone group. In Ohta's report, chemotherapy had to be administered for two or three courses, and many patients received only two cycles of chemotherapy, only 41% of the patients received three cycles of chemotherapy. In the present protocol, cycles of chemotherapy should be administered three times because the low compliance of drug delivery might have contributed to the negative result of the study of Ohta et. al. Also, the present protocol included only N2 patients so as to make the population more uniform.

2. Patients and methods

The protocol was reviewed by JCOG Clinical Trial Review Committee and approved by the Institutional Review Board of each participating hospital. Patient eligibility was dependent on the following criteria: to have undergone complete resection with systematic mediastinal dissection (as described in "General rule for clinical and pathological record of lung cancer" [4]), histologically documented non-small cell lung cancer, including squamous cell carcinoma, adenocarcinoma, large cell carcinoma or adeno-squamous cell carcinoma; age less than 75 years and World Health Organization (WHO) performance status 0-1; normal hematological data (WBC $\geq$ *4000*/mm^3, platelet count $\geq$100,000/mm^3); normal hepatic function (bilirubin $\leq$1.5 mg/dl, SGOT and SGPT within twice the normal range); and normal renal function (blood urea nitrogen $\leq$25 mg/dl, serum creatinine $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min). Furthermore, to be eligible, the absence of no distant metastasis prior to surgery had to be established by full staging procedures including brain computed tomography (CT) or magnetic resonance imaging (MRI), chest CT, bone scans, and abdominal CT or abdominal ultrasonography revealed. Mediastinoscopy was not mandatory before surgery. All patients had ipsilateral mediastinal lymph node metastasis. Finally, patients could not have been previously treated with chemotherapy or radiation therapy for any malignancy and could not have active secondary cancers. Written informed consent, signed by patients, was mandatory before registration.

The following were excluded.: low-grade malignant lung cancers such as carcinoid tumor, adenoid cystic carcinoma or mucoepidermoid carcinoma, N3 lymph node metastases (contralateral mediastinal, contralateral hilar, supraclavicular nodes, or scalene nodes) and cases with malignant pleural effusion or pleural dissemination, T4 disease, i.e. direct invasion to the mediastinal lymph nodes, esophagus, vertebral bodies, heart or carina. Patients with Pancoast type tumor; superior vena cava syndrome or pretracheal or paratracheal lymph node metastases from cancers in which the primary lesion was located in the left lung were also excluded.

At post-operative registration, patients were randomly assigned to either observation or adjuvant chemotherapy. Neither group was allowed to receive any other treatments for cancer other than the planned adjuvant chemotherapy until relapse.

The adjuvant chemotherapy regimen was as follows: intravenous cisplatin (CDDP) 80 mg/m^2 on day 1 and vindesine (VDS) 3 mg/m^2 on days 1 and 8, every 4 weeks for 3 cycles. Chemotherapy started within 6 weeks after surgery.