The degree of myelosuppression in the IP regimens was less than that of the EP regimens. However, diarrhoea was more often observed in the IP than the EP regimens, and can lead to severe side effects when the IP regimen is used incautiously. Pharmacogenetic study of irinotecan may prompt one to use the drug in a safer way to avoid severe toxicities. McLeod suggests that at the least, irinotecan 300 – 350 mg/m^2 every 3 weeks should not be given to patients with a known UGT1A1*28 genotype until more definitive guidelines are established [60]. However, the use of UGT1A1*28 genotyping to predict toxicity is controversial and its clinical implications are unclear. Furthermore, whether or not these recommendations are also applicable to patients with SCLC should be elucidated upon because a lower dose of irinotecan is usually administered weekly for the treatment of SCLC, rather than the every 3 or 4 weeks for colorectal cancers. In the coming decade, we must confront the metabolic and pharmacogenomic differences in various populations for the treatment of cancer. For this, international cooperative studies are warranted and indeed of immense importance.

Considering patient safety, irinotecan can indeed be administered relatively safety in patients with SCLC, provided there is careful monitoring of patients, especially regarding diarrhoea and myelosuppresion. Further studies to avoid severe toxicities are needed to advance the safe use of this otherwise promising drug.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. PISANI P, PARKIN DM, BRAY F, FERLAY J: Estimates of the worldwide mortality from 25 cancers in 1990. *Int. J. Cancer* (1999) 83:18-29.
2. PAGE N, READ W, TIERNEY R, ARQUETTE M, PICCIRILLO J, GOVINDAN R: The epidemiology of small cell lung canrcinoma. *Proc. Am. Soc. Clin. Oncol.* (2002) 21:305 (Abstract 1216).
3. STUPP R, MONNERAT C, TURRISI AT, 3rd, PERRY MC, LEYVRAZ S: Small cell lung cancer: state of the art and future perspectives. *Lung Cancer* (2004) 45(1):105-117.

•• **State of art of SCLC.**

4. COMIS RL, FRIEDLAND DM, GOOD BC: Small-cell lung cancer: a perspective on the past and a preview of the future. *Oncology* (1998) 12(1 Suppl 2):44-50.
5. WOLF M, TEBBE S, FINK T: First-line chemotherapy in metastatic small-cell lung cancer (SCLC). *Lung Cancer* (2004) 45(Suppl. 2):S223-S234.
6. IYER L, KING CD, WHITINGTON PF *et al.*: Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. *J. Clin. Invest.* (1998) 101(4):847-854.

• **Role of UGT1A1 in the glucuronidation of SN-38.**

7. MCLEOD HL: Drug pathways: moving beyond single gene pharmacogenetics. *Pharmacogenomics* (2004) 5(2):139-141.
8. SPARREBOOM A, DANESI R, ANDO Y, CHAN J, FIGG WD: Pharmacogenomics of ABC transporters and its role in cancer chemotherapy. *Drug Resist. Updat.* (2003) 6(2):71-84.
9. MARSH S, MCLEOD HL: Pharmacogenetics of irinotecan toxicity. *Pharmacogenomics* (2004) 5(7):835-843.
10. MA MK, MCLEOD HL: Lessons learned from the irinotecan metabolic pathway. *Curr. Med. Chem.* (2003) 10(1):41-49.
11. DE JONG FA, DE JONGE MJ, VERWEIJ J, MATHIJSSEN RH: Role of pharmacogenetics in irinotecan therapy. *Cancer Lett.* (2005) Epub ahead of print.
12. TAKIMOTO CH: Chapter 15: *Pharmacology of Cancer Chemotherapy*: Section 7: Topoisomerase Interactive Agents. 7th Ed., Philadelphia: Lippincott Williams & Wilkins (2005):375-390.
13. KUHN JG: Influence of anticonvulsants on the metabolism and elimination of irinotecan. A North American Brain Tumor Consortium preliminary report. *Oncology* (2002) 16(8 Suppl. 7):33-40.
14. YONEMORI K, TAKEDA Y, TOYOTA E, KOBAYASHI N, KUDO K: Potential interactions between irinotecan and rifampin in a patient with small-cell lung cancer. *Int. J. Clin. Oncol.* (2004) 9(3):206-209.
15. MATHIJSSEN RH, VERWEIJ J, DE BRUIJN P, LOOS WJ, SPARREBOOM A: Effects of St. John's wort on irinotecan metabolism. *J. Natl. Cancer Inst.* (2002) 94(16):1247-1249.
16. KEHRER DF, MATHIJSSEN RH, VERWEIJ J, DE BRUIJN P, SPARREBOOM A: Modulation of irinotecan metabolism by ketoconazole. *J. Clin. Oncol.* (2002) 20(14):3122-3129.
17. OHE Y: Treatment-related death from chemotherapy and thoracic radiotherapy for advanced cancer. *Panminerva Med.* (2002) 44(3):205-212.
18. ABIGERGES D, ARMAND JP, CHABOT GG *et al.*: Irinotecan (CPT-11) high-dose escalation using intensive high-dose loperamide to control diarrhea. *J. Natl. Cancer. Inst.* (1994) 86(6):446-449.

• **Effect of high-dose loperamide for diarrhoea induced by irinotecan.**

19. ARMAND JP, TERRET C, COUTEAU C, RIXE O: CPT-11. The European experience. *Ann. N Y Acad. Sci.* (1996) 803:282-291.
20. KUDOH S, FUJIWARA Y, TAKADA Y *et al.*: Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer. West Japan Lung Cancer Group. *J. Clin. Oncol.* (1998) 16(3):1068-1074.

• **Activity of irinotecan and cisplatin for SCLC as front-line.**

21. KUBOTA K, NISHIWAKI Y, SUGIURA T *et al.*: Pilot study of concurrent etoposide and cisplatin plus accelerated hyperfractionated thoracic radiotherapy followed by irinotecan and cisplatin for limited-stage small cell lung cancer: Japan Clinical Oncology Group 9903. *Clin. Cancer Res.* (2005) 11(15):5534-5538.

• **IP following chemoradiotherapy for LD SCLC.**

22. VON PAWEL J, SCHILLER JH, SHEPHERD FA *et al.*: Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J. Clin. Oncol.* (1999) 17(2):658-667.

23. VON PAWEL J: The role of topotecan in treating small cell lung cancer: second-line treatment. *Lung Cancer* (2003) **41**(Suppl. 4):S3-S8.

24. NEGORO S, FUKUOKA M, NIITANI H, TAGUCHI T: Phase II study of CPT-11, new camptothecin derivative, in small cell lng cancer (SCLC) (abstract). *Proc. Am. Soc. Clin. Oncol.* (1991) **10**:214.

25. MASUDA N, FUKUOKA M, KUSUNOKI Y *et al.*: CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J. Clin. Oncol.* (1992) **10**(8):1225-1229.

• **Activity of irinotecan for relapsed SCLC.**

26. NODA K, NISHIWAKI Y, KAWAHARA M *et al.*: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N. Engl. J. Med.* (2002) **346**(2):85-91.

•• **First report of superiority of IP to EP.**

27. HANNA NH, EINHORN L, SANDLER A *et al.*: Randomized, phase III trial comparing irinotecan/cisplatin (IP) with etoposide/cisplatin (EP) in patients (pts) with previously untreated, extensive-stage (ES) small cell lung cancer (SCLC). *Proc. Am. Soc. Clin. Oncol.* (2005) **23**:622s.

• **IP is equivalent to EP.**

28. TAKIGAWA N, FUJIWARA K, UEOKA H *et al.*: Fractionated administration of irinotecan and cisplatin for treatment of extensive-disease small-cell lung cancer: a phase II study. *Anticancer Res.* (2003) **23**(1B):557-560.

29. HAN JY, LEE DH, LEE SY *et al.*: A phase II study of dose-intensified weekly concomitant administration of cisplatin and irinotecan in chemonaive patients with extensive-disease small-cell lung cancer. *Med. Oncol.* (2005) **22**(3):281-290.

30. SCHMITTEL A, SCHULZE K, HUTTER G, KREBS P, THIEL E, KEILHOLZ U: Phase I dose escalation study of carboplatin to a fixed dose of irinotecan as first-line treatment of small cell lung cancer. *Onkologie* (2004) **27**(3):280-284.

31. FUKUDA M, OKA M, SODA H *et al.*: Phase I study of irinotecan combined with carboplatin in previously untreated solid cancers. *Clin. Cancer Res.* (1999) **5**(12):3963-3969.

32. SCHMITTEL A, FISCHER VON WEIKERSTHAL L, SEBASTIAN M *et al.*: Irinotecan plus carboplatin versus etoposide plus carboplatin in extensive disease small cell lung cancer: A randomized phase II trial. *Proc. Am. Soc. Clin. Oncol.* (2005) **23**:632s.

33. KUDOH S, NAKAMURA S, NAKANO T *et al.*: Irinotecan and etoposide for previously untreated extensive-disease small cell lung cancer: a phase II trial of West Japan Thoracic Oncology Group. *Lung Cancer* (2005) **49**(2):263-269.

34. SEKINE I, NISHIWAKI Y, NODA K *et al.*: Randomized phase II study of cisplatin, irinotecan and etoposide combinations administered weekly or every 4 weeks for extensive small-cell lung cancer (JCOG9902-DI). *Ann. Oncol.* (2003) **14**(5):709-714.

• **Three drug combination for ED SCLC.**

35. BRIASOULIS E, SAMANTAS E, KALOFONOS H *et al.*: Phase I study of etoposide, cisplatin and irinotecan triplet in patients with advanced-stage small-cell lung cancer. *Cancer Chemother. Pharmacol.* (2005) **56**(5):521-528.

36. SAMANTAS E, SYRIGOS K, BRIASOULIS E *et al.*: Phase II study of cisplatin plus etoposide over 3 days combined with irinotoecan and early thoracic radiotherapy (TRT) in patients with limited disease (LD) small cell lung cancer (SCLC), preliminary results. *Lung Cancer* (2005) **49**(Suppl. 2):S327.

37. THOMPSON DS, HAINSWORTH JD, SPIGEL DR *et al.*: Irinotecan (I), carboplatin (C), and imatinib (IM) in the first-line treatment of extensive-stage small cell lung cancer (SCLC): a phase II trial of the Minnie Pearl Cancer Research Network. *Proc. Am. Soc. Clin. Oncol.* (2005) **23**:632s.

38. HUISMAN C, POSTMUS PE, GIACCONE G, SMIT EF: Second-line chemotherapy and its evaluation in small cell lung cancer. *Cancer Treat. Rev.* (1999) **25**(4):199-206.

39. ANDO M, KOBAYASHI K, YOSHIMURA A *et al.*: Weekly administration of irinotecan (CPT-11) plus cisplatin for refractory or relapsed small cell lung cancer. *Lung Cancer* (2004) **44**(1):121-127.

40. NAKA N, KAWAHARA M, OKISHIO K *et al.*: Phase II study of weekly irinotecan and carboplatin for refractory or relapsed small-cell lung cancer. *Lung Cancer* (2002) **37**(3):319-323.

41. HIROSE T, HORICHI N, OHMORI T *et al.*: Phase II study of irinotecan and carboplatin in patients with the refractory or relapsed small cell lung cancer. *Lung Cancer* (2003) **40**(3):333-338.

42. MASUDA N, MATSUI K, NEGORO S *et al.*: Combination of irinotecan and etoposide for treatment of refractory or relapsed small-cell lung cancer. *J. Clin. Oncol.* (1998) **16**(10):3329-3334.

43. AGELAKI S, SYRIGOS K, CHRISTOPHYLAKIS C *et al.*: A multicenter phase II study of the combination of irinotecan and gemcitabine in previously treated patients with small-cell lung cancer. *Oncology* (2004) **66**(3):192-196.

44. SCHUETTE W, NAGEL S, JUERGENS S *et al.*: Phase II trial of gemcitabine/Irinotecan in refractory or relapsed small-cell lung cancer. *Clin. Lung Cancer* (2005) **7**(2):133-137.

45. ICHIKI M, GOHARA R, RIKIMARU T *et al.*: Combination chemotherapy with irinotecan and ifosfamide as second-line treatment of refractory or sensitive relapsed small cell lung cancer: a phase II study. *Chemotherapy* (2003) **49**(4):200-205.

46. RUSHING DA: Phase I/II study of weekly irinotecan and paclitaxel in patients with SCLC. *Oncology* (Huntingt) (2000) **14**(7 Suppl. 5):63-66.

47. SEKINE I, NISHIWAKI Y, KAKINUMA R *et al.*: Phase I/II trial of weekly cisplatin, etoposide, and irinotecan chemotherapy for metastatic lung cancer: JCOG 9507. *Br. J. Cancer* (2003) **88**(6):808-813.

48. GOTO K, SEKINE I, NISHIWAKI Y *et al.*: Multi-institutional phase II trial of irinotecan, cisplatin, and etoposide for sensitive relapsed small-cell lung cancer. *Br. J. Cancer* (2004) **91**(4):659-665.

• **Three drug combination for sensitive relapsed SCLC.**

49. FUJITA A, TAKABATAKE H, TAGAKI S, SEKINE K: Combination of cisplatin, ifosfamide, and irinotecan with rhG-CSF support for the treatment of refractory or relapsed small-cell lung cancer. *Oncology* (2000) **59**(2):105-109.

50. PIGNON JP, ARRIAGADA R, IHDE D *et al.*: A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N. Engl. J. Med.* (1992) **327**:1618-1624.

51. WARDE P, PAYNE D: Does thoracic irradiation improve survival and local control in limited- stage small-cell carcinoma of the lung? *J. Clin. Oncol.* (1992) 10:890-895.

52. MURRAY N: Treatment of small cell lung cancer: the state of the art. *Lung Cancer* (1997) 17(Suppl 1):S75-S89.

53. TURRISI AT, KIM K, BLUM R *et al.*: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N. Engl. J. Med.* (1999) 340:265-271.

54. TAMURA K, TAKADA M, KAWASE I *et al.*: Enhancement of tumor radio-response by irinotecan in human lung tumor xenografts. *Jpn. J. Cancer Res.* (1997) 88(2):218-223.

55. KASHII T, SAITO H, NEGORO S *et al.*: Phase II study of cisplatin plus etoposide with concurrent thoracic radiotherapy (TRT) followed by irintoecan plus cisplatin in limited stage small-cell lung cancer (SCLC); A West Japan Thoracic Oncology Group Trial. *Lung Cancer* (2005) 49(Suppl. 2):S322.

56. HAN JY, CHO KH, LEE DH *et al.*: Phase II study of irinotecan plus cisplatin induction followed by concurrent twice-daily thoracic irradiation with etoposide plus cisplatin chemotherapy for limited-disease small-cell lung cancer. *J. Clin. Oncol.* (2005) 23(15):3488-3494.

57. RAEFSKY EL, SPIGEL DR, GRECO FA *et al.*: Irinotecan (I), carboplatin (C), and radiotherapy (RT) followed by bevacizumab (B) in the treatment of limited-stage small cell lung cancer (SCLC): a phase II trial of the Minnie Pearl Cancer Research Network. *Proc. Am. Soc. Clin. Oncol.* (2005) 23:633s.

- **Irinotecan, carboplatin and concurrent RT for LD SCLC.**

58. SOHN J, MOON Y, LEE C *et al.*: Phase II trial of irinotecan and cisplatin with concurrent radiotherapy in limited-disease small cell lung cancer. *Proc. Am. Soc. Clin. Oncol.* (2005) 23:662s.

- **Irinotecan, cisplatin and concurrent RT for LD SCLC.**

59. LANGER C, SWANN S, WERNER-WASIK M *et al.*: Phase I study of combination irinotecan and cisplatin and either twice daily thoracic radiation (45Gy) or once daily thoracic radiotherapy (70Gy) in patients with limited small cell lung carcinoma (SCLC): Early toxicity analysis of RTOG 0241. *Lung Cancer* (2005) 49(Suppl. 2):S323.

60. MCLEOD HL, WATTERS JW: Irinotecan pharmacogenetics: is it time to intervene? *J. Clin. Oncol.* (2004) 22(8):1356-1359.

- **Editorial for irinotecan pharmacogenetics.**

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ORIGINAL REPORT

First-Line Single Agent Treatment With Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer: A Phase II Study

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ABSTRACT

Purpose
We conducted a phase II study of single agent treatment with gefitinib in chemotherapy-naïve patients with advanced non–small-cell lung cancer (NSCLC) to assess its efficacy and toxicity.

Patients and Methods
Patients received 250 mg doses of gefitinib daily. Administration of gefitinib was terminated if partial response (PR) was not achieved within 8 weeks or if tumor reduction was not observed within 4 weeks. In these cases, platinum-based doublet chemotherapy was given as a salvage treatment. We evaluated mutation status of the epidermal growth factor receptor (EGFR) gene in cases with available tumor samples.

Results
Forty-two patients were enrolled between March and November 2003, with 40 of these patients being eligible. The response rate was 30% (95% CI, 17% to 47%). The most common toxicity included grade 1 or 2 acne-like rash (50%) and grade 1 diarrhea (18%). Grade 2 or 3 hepatic toxicity was observed in 8% of patients. Four patients developed grade 5 interstitial lung disease (ILD). Thirty patients received second-line chemotherapy. Median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55%. Tumor samples were available in 13 patients, including four cases of PR, six cases of stable disease, and three cases of progressive disease. *EGFR* mutations (deletions in exon 19 or point mutations [L858R or E746VI]) were detected in four tumor tissues. All four patients with *EGFR* mutation achieved PR with gefitinib treatment.

Conclusion
Single agent treatment with gefitinib is active in chemotherapy-naïve patients with advanced NSCLC, but produces unacceptably frequent ILD in the Japanese population.

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INTRODUCTION

Previous meta-analysis demonstrated that cisplatin-based chemotherapy yielded a modest but significant survival benefit over best supportive care in advanced non–small-cell lung cancer (NSCLC).[1-4] In the 1990s, new agents, including vinorelbine, gemcitabine, paclitaxel, docetaxel, and irinotecan became available for the treatment of NSCLC. Several phase III trials comparing doublet platinum-based chemotherapies demonstrated no significant difference with respect to response rate, survival, or quality of life.[5,6] Nonplatinum or triplet platinum-based combination chemotherapies have been investigated, but none of these produced longer survival than standard doublet platinum-based chemotherapy.[7-9]

Recently, molecular-targeted agents have been introduced for the treatment of NSCLC. Gefitinib is an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, which displays activity against recurrent NSCLC after platinum-based chemotherapy. Two international, randomized phase II trials in patients with advanced or metastatic NSCLC after platinum-based chemotherapy demonstrated response rates of 12% to 18% (28% in the Japanese population).[10,11] Two international, randomized, double-blinded, placebo-controlled phase III trials investigated the role of gefitinib combined with platinum-based chemotherapy regimens, including carboplatin and paclitaxel, or cisplatin and gemcitabine in chemotherapy-naïve patients with advanced NSCLC.[12,13] Surprisingly, there were no improvements in overall survival,

time to progression, or response rate. There are no data available regarding first-line treatment with single agent gefitinib against NSCLC in the Japanese population. Here, we conducted a phase II study of single agent treatment with gefitinib in chemotherapy-naïve patients with advanced NSCLC. If a failure with gefitinib treatment was perceived, standard platinum-based doublet chemotherapy was performed as salvage. The primary end point of this phase II trial was response rate, and the secondary end points were toxicity, survival, and response rate of salvage chemotherapy.

PATIENTS AND METHODS

Patient Population

Patients were required to have histologically or cytologically confirmed stage IIIB (malignant pleural or pericardial effusion and/or metastasis in the same lobe) or stage IV NSCLC. Recurrences after surgical resection were permitted. Other criteria included: (1) age 20 years or older, but younger than 75 years; (2) Eastern Cooperative Oncology Group performance status (PS) 0 or 1; (3) measurable disease; (4) PaO2 $\geq$ 60 mmHg; (5) adequate organ function (ie, total bilirubin $\leq$ 2.0, AST and ALT $\leq$ 100 U/L, serum creatinine $\leq$ 1.5 mg/dL, leukocyte count 4,000 to 12,000/mm^3, neutrophil count $\geq$ 2,000/mm^3, hemoglobin $\geq$ 9.5 g/dL, and platelets $\geq$ 100,000/mm^3); (6) no prior chemotherapy or thoracic radiotherapy; (7) no interstitial pneumonia or pulmonary fibrosis, as determined by chest x-ray; (8) no paralytic ileus or vomiting, (9) no symptomatic brain metastases, (10) no active infection; (11) no active concomitant malignancy; (12) no pregnancy or breast-feeding; (13) no severe allergy to drugs. Patients with PaO2 less than 60 mmHg were excluded, because those patients might have pulmonary fibrosis, which is a risk factor of interstitial lung disease (ILD).[14] All patients were required to provide written informed consent and the institutional review board at the National Cancer Center approved the protocol.

Treatment Plan

Treatment was started within a week after enrollment in the study. Patients received 250 mg of gefitinib orally daily. In the event of grade 3 or more and/or unacceptable toxicities, gefitinib was postponed until these toxicities were improved to grade 2 or less. Dose reduction was not performed. If treatment was postponed four times or more, the treatment was terminated. Therapy was continued unless the patient experienced unacceptable toxicity or progressive disease, partial response (PR) was not achieved within 8 weeks, or the sum of the longest diameters of the target lesions decreased less than 10% within 4 weeks. If the gefitinib treatment failed according to these criteria, platinum-based doublet chemotherapy was performed as a salvage regimen.

Previous trials of gefitinib for pretreated patients with NSCLC reported that most responding patients showed rapid tumor regression within 4 or 8 weeks.[11] Furthermore, most responses by gefitinib were extreme shrinkage of the tumor. Minor response, as frequently seen by the treatment with cytotoxic agents, was seldom experienced. Stable disease with gefitinib corresponded to no tumor reduction or slight progression. If patients with stable disease continued the treatment with gefitinib until progressive disease became obvious, those patients might not be able to receive platinum-based salvage chemotherapy because of poor PS due to progressive disease. Platinum-based combination chemotherapy is the standard care for patients with advanced NSCLC and good PS. Platinum-based chemotherapy was thought to be essential for patients with no response from the first-line single agent treatment with gefitinib. Therefore, we implemented these early stopping criteria for treatment with gefitinib.

Study Evaluations

Pretreatment evaluations consisted of a complete medical history, determination of performance status, physical examination, hematologic and biochemical profiles, arterial blood gas examination, ECG, chest x-ray, bone scan, and computed tomography (CT) scan of the chest, ultrasound or CT scan of the abdomen, and magnetic resonance imaging or CT scan of the whole brain. Evaluations performed included a weekly chest x-ray for 4 weeks, and once every 2 weeks for biochemistry, complete blood cell, platelet, leukocyte differential counts, physical examination, determination of performance status, and toxicity assessment. Imaging studies were scheduled to assess objective response every month.

Response and Toxicity Criteria

Response evaluation criteria in solid tumors (RECIST) guidelines were used for evaluation of antitumor activity.[15] The target lesions were defined as $\geq$ 2 cm in the longest diameter on CT scans. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A PR was defined as an at least 30% decrease in the sum of the longest diameters of the target lesions for more than 4 weeks with no new area of malignant disease. Progressive disease (PD) indicated at least a 20% increase in the sum of the longest diameter of the target lesions or a new malignant lesion. Stable disease was defined as insufficient shrinkage to qualify for PR and insufficient increase to qualify for PD. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Mutation Analysis of the EGFR Gene

Tumor specimens were obtained during diagnostic or surgical procedures. Biopsied or surgically resected specimens were fixed with formalin or 100% methanol, respectively. Tumor genomic DNA was prepared from paraffin-embedded sections using laser capture microdissection in biopsied specimens or macrodissection in surgically resected specimens at Mitsubishi Chemical Safety Institute LTD. Exons 18, 19, and 21 of the *EGFR* gene were amplified and sequenced as previously described.[16]

Statistical Analysis

In accordance with the minimax two-stage phase II study design by Simon,[17] the treatment program was designed to refuse response rates of 10% (P_0) and to provide a significance level of .05 with a statistical power of 80% in assessing the activity of the regimen as a 25% response rate (P_1). The upper limit for first-stage drug rejection was two responses in the 22 assessable patients; the upper limit of second-stage rejection was seven responses within the cohort of 40 assessable patients. Overall survival was defined as the interval between enrollment in this study and death or the final follow-up visit. Median overall survival was estimated by the Kaplan-Meier analysis method.[18] Fisher's exact test was used in a contingency table.

RESULTS

Patient Population

A total of 42 patients were enrolled in this study between March and November, 2003, with 40 of these patients being eligible. One patient was found ineligible due to anemia, the other because spinal magnetic resonance imaging could not confirm a positive bone scan. Patient characteristics are listed in Table 1. Sixty percent of patients were male; median age was 61 years. The most common histologic subtype was adenocarcinoma (75%). Most patients (93%) had stage IV disease or recurrence after surgical resection. Eighty percent of patients were current or former smokers.

Efficacy

One patient (3%) has been receiving gefitinib after 22 months. Four patients suspended gefitinib for 11, 14, 27, or 29 days, because of liver dysfunction (n = 3) and fever due to urinary tract infection (n = 1). Thirty-nine patients terminated gefitinib because of progressive disease (n = 20), no tumor reduction within 4 weeks (n = 12), not achieving PR within 8 weeks (n = 1), toxicities including pulmonary (n = 3), nausea and vomiting (n = 1), rash (n = 1), or hepatic dysfunction (n = 1).

There were 12 PRs in 40 eligible patients, and the objective response rate was 30% (95% CI, 17% to 47%; Table 2). All but one

Table 1. Patient Characteristics

Characteristic	No. of Patients
Patients enrolled	42
Patients eligible	40
Sex	
Male	24
Female	16
Age, years	
Median	61
Range	44-74
Performance status	
0	14
1	26
Stage	
IIIB	3
IV	34
Recurrence after surgery	3
Histologic type	
Adenocarcinoma	30
Squamous cell carcinoma	3
Large cell carcinoma	7
Smoking history	
Current	27
Former	5
Never	8

patient from this subgroup achieved PR within 4 weeks, with the remaining patient achieving PR within 8 weeks. The background of the 12 responding patients was as follows: nine females, three males; 11 adenocarcinomas, one large-cell carcinoma; six individuals who never smoked, five current smokers, and one former smoker. Response rates based on patient characteristics were as follows: three of 24 (13%) males, nine of 16 (56%) females ($P = .0050$); 11 of 30 (37%) individuals with adenocarcinoma, one of 10 (10%) individuals with squamous or large-cell carcinoma ($P = .0048$); six of 32 (19%) current or former smokers, and six of eight (75%) individuals who never smoked ($P = .0048$).

The median follow-up time was 23 months, and nine patients were still alive at the most recent follow-up. The median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55% (Fig 1).

Safety and Toxicity

Toxicity was evaluated in all eligible patients. The most common toxicity was rash (Table 3). Thirty-eight percent and 13% of patients

Table 2. Efficacy of Single Agent Treatment With Gefitinib in Patients With Stage IIIb or IV Non–Small-Cell Lung Cancer

Type of Response	No. of Patients	% of Patients
Complete	0	0
Partial	12	30
CR + PR	12	30
95% CI	17 to 47	
Stable disease	16	40
Progression	12	30

Abbreviations: CR, complete response; PR, partial response.

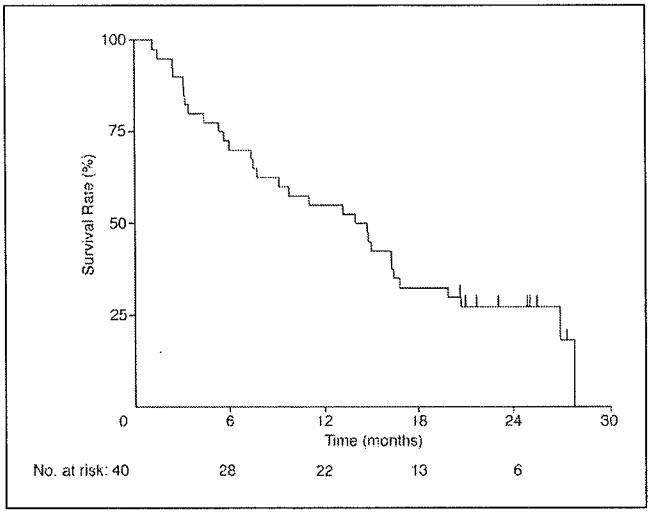

Fig 1. Overall survival of all eligible patients (n = 40) was calculated according to the Kaplan-Meier method. The median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55%.

experienced grade 1 or 2 rash, respectively. One patient experienced grade 3 nausea and vomiting, leading to gefitinib treatment being terminated. Grade 3 hepatic toxicity was observed in one patient, also causing termination of gefitinib treatment.

The most problematic toxicity was ILD. We reviewed the medical records, chest x-rays, and CT films of all the cases, which were suspected as ILD by the physician in charge. ILD was diagnosed on the basis of standard or high-resolution CT findings of the chest (diffuse ground-glass opacity, consolidation, or infiltrate) and no response to antibiotics. We diagnosed that four patients experienced grade 5 ILD during or after first-line treatment with gefitinib. The first patient was a 61-year-old man. He developed dyspnea and fever elevation (38.1°C) on day 23 of the treatment with gefitinib and administration of gefitinib was terminated. Chest CT demonstrated bilateral diffuse ground-glass opacity, and PaO2 was 43.7mmHg in the room air. KL-6 antigen, a serum marker of interstitial pneumonia, was not elevated

Table 3. Maximum Toxicity Grades Associated With Single Agent Treatment With Gefitinib in 40 Patients With Non–Small-Cell Lung Cancer

	Toxicity Grade									
	1		2		3		4		5	
Toxicity	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Rash	15	38	5	13	0	0	0	0	0	0
Dry skin	4	10	0	0	0	0	0	0	0	0
Diarrhea	7	18	0	0	0	0	0	0	0	0
Nausea	3	8	0	0	1	3	0	0	0	0
Mucositis	6	15	0	0	0	0	0	0	0	0
Alopecia	4	10	0	0	0	0	0	0	0	0
Hyponatremia	24	60	0	0	3	8	0	0	0	0
Hypokalemia	12	30	0	0	0	0	0	0	0	0
Hepatic	11	28	2	5	1	3	0	0	0	0
Renal	4	10	1	3	0	0	0	0	0	0
ILD	0	0	0	0	0	0	0	0	4	10

Abbreviation: ILD; interstitial lung disease.

(351 U/mL) on day 24, but elevated on day 31 (1,400 U/mL). Beta-D-glucan, a serum marker of fungal infection and *Pneumocystis carinii* pneumonia, was also negative. Methylprednisolone and antibiotics were administered, with temporal improvement of ILD. However, subsequently, pulmonary function gradually deteriorated, leading to death. Autopsy revealed alveolar damage with organization around the bronchus and vessels in both neoplastic and non-neoplastic lesions, compatible with drug-induced ILD. The second patient was a 64-year-old man. Chest CT on day 27 showed stable disease, but administration of gefitinib was continued (protocol violation). Periodic chest x-ray film on day 45 showed abnormal shadow in the left lung field. High-resolution CT of the chest on the same day revealed reticular shadow on bilateral upper lobe. The treatment with gefitinib was terminated on day 45. KL-6 antigen was not elevated on day 49 (276 U/mL). Methylprednisolone and antibiotics were administered, but were not effective, leading to death. The third patient was a 67-year-old man. Chest CT on day 30 demonstrated enlargement of primary lesion and bilateral reticular shadow in subpleural lesions. Gefitinib was terminated on day 30. The patient developed dyspnea without fever elevation on day 37. Pao2 in the room air fell to 61.0 mmHg from 82.4 mmHg at pretreatment. Chest x-ray showed that the bilateral diffuse reticular shadow deteriorated. Methylprednisolone and antibiotics were administered, but were not effective, leading to death. Autopsy revealed severe fibrotic thickness of alveolar septum, compatible with severe interstitial pneumonia. There was no pathological evidence of carcinomatous lymphangiosis. The fourth patient was a 59-year-old woman. Chest x-ray showed consolidation in the left lung on day 21. Slight fever (37.9°C) developed on day 22. Blood culture was negative. Antibiotics were administered, but consolidation deteriorated and spread to both lungs on day 25. Gefitinib was terminated on day 25. KL-6 antigen was elevated to 3,590 U/mL. Methylprednisolone was administered, but was not effective, leading to death (Table 4). Four other patients experienced ILD after second-line or third-line chemotherapy. Two patients received second-line treatment with cisplatin plus vinorelbine (one and four courses), one patient received treatment with cisplatin plus gemcitabine (one course), and one patient received third-line treatment with docetaxel (four courses). Three of four patients received steroids, with temporal improvement of ILD being observed in two patients. However, ILD deteriorated during tapering of steroid treatment, with three patients subsequently dying. One patient stopped the third-line treatment with docetaxel, with the associated ILD showing improvement in this case without steroid treatment (Table 4).

We retrospectively reviewed the pretreatment chest x-rays and CT films of all patients. Interstitial shadow was not detected on pretreatment chest x-ray films in any patients. However, six patients showed evidence of interstitial shadow on pretreatment chest CT films. Three of the six patients with interstitial shadow, as determined by pretreatment chest CT, experienced ILD either during or following administration of gefitinib or second-line chemotherapy. None of the six patients responded to gefitinib treatment. On the other hand, four of 34 patients who showed no interstitial shadow on pretreatment chest CT films experienced ILD. Interstitial shadow as determined by pretreatment chest CT was not a statistically significant risk factor of ILD ($P = .0819$; Table 5).

Second-Line Chemotherapy

A total of 30 patients received second-line chemotherapy. Twenty-seven patients received platinum-based chemotherapy (cisplatin plus vinorelbine; n = 17), carboplatin plus paclitaxel (n = 5), cisplatin plus gemcitabine (n = 3), cisplatin plus docetaxel (n = 1), and cisplatin plus irinotecan (n = 1). The remaining three patients received vinorelbine plus gemcitabine or vinorelbine alone. Nine of 30 patients achieved PR with these second-line chemotherapies. The objective response rate of second-line chemotherapy was 30% (95% CI, 15% to 50%).

Mutation Status of the EGFR Gene

Out of 42 enrolled patients, 16 patients were diagnosed pathologically, 22 were diagnosed cytologically, and four patients recurred after surgical resection. Biopsied specimens were available in nine patients. Therefore, tissue samples were available in a total of 13 patients. These 13 patients included four PRs, six with stable disease, and three PDs. *EGFR* mutations were detected in four tumor tissues, including the in-frame nucleotide deletions in exon 19 (n = 3) and an L858R mutation in exon 21 (n = 1). One tumor had an in-frame deletion and

Table 4. Four Patients Developed Interstitial Lung Disease During First-Line Chemotherapy With Gefitinib, With Another Four Patients Showing ILD During Either Second- or Third-Line Chemotherapy

Age (years)	Sex	Smoking Index	Pathology	Onset of ILD	Response to Gefitinib	Death From Chemotherapy
61	M	1,520	AD	Day 23*	PD	Day 74
64	M	880	AD	Day 45*	SD	Day 51
67	M	1,880	SQ	Day 37†	PD	Day 45
59	F	0	AD	Day 21*	PD	Day 35
61	M	820	AD	Day 131‡	SD	Day 154
68	M	2,000	LA	Day 37‡	PD	Day 106
68	M	705	AD	Day 22§	PR	Day 87
59	M	1,170	AD	Day 108‖	SD	Alive

Abbreviations: ILD, interstitial lung disease; M, male; F, female; AD, adenocarcinoma; SQ, squamous cell carcinoma; LA, large-cell carcinoma; PD, progressive disease; SD, stable disease; PR, partial response.
*During gefitinib administration.
†One week after discontinuation of gefitinib.
‡ After 2nd-line chemotherapy of cisplatin and vinorelbine.
§ After 2nd-line chemotherapy of cisplatin and gemcitabine.
‖ After 3rd-line chemotherapy of docetaxel.

Table 5. Interstitial Shadow on Pretreatment Chest Computed Tomography Films and ILD

Interstitial Shadow on Pretreatment Chest Computed Tomography Scans	No ILD	ILD
No existence	29	5
Existence	3	3

NOTE. $P = .0819$.
Abbreviation: ILD interstitial lung disease.

an E746V mutation in exon 19. All four PR patients had *EGFR* mutations (Table 6).

DISCUSSION

This phase II study was designed to evaluate the efficacy and safety of first-line single agent treatment with gefitinib in patients with advanced NSCLC. There is no other paper that evaluates single agent treatment with gefitinib prospectively in patients with advanced NSCLC. The observed response rate of 30% (95% CI, 17% to 47%), median survival of 13.9 months and 1-year survival of 55% are promising. However, grade 5 ILD occurred in 10% (95% CI, 3% to 24%) of patients. This high rate of ILD was not acceptable. The incidence of ILD was seen to be less than 1% in two randomized controlled studies comparing gefitinib with placebo in combination with gemcitabine and cisplatin or paclitaxel and carboplatin.[12,13] The reason for the high incidence of ILD observed in our study is unknown. The West Japan Thoracic Oncology Group analyzed 1,976 patients receiving gefitinib retrospectively. In this case, the incidence of ILD was 3.2% (95% CI, 2.5% to 4.6%) and the death rate due to ILD was 1.3% (95% CI, 0.8% to1.9%). Multivariate analyses found that risk factors included being male, individuals who smoked, and complication of interstitial pneumonia.[14] Our retrospective analyses revealed that three of six patients with interstitial shadow on pretreatment chest CT films, but not detected on chest x-ray films developed ILD; on the other hand, five of 34 patients without interstitial shadow developed ILD. Interstitial shadow on pretreatment chest CT was a marginally significant risk factor of ILD ($P = .0819$). It might be suggested that patients with interstitial shadow on pretreatment chest CT films be excluded from administration of gefitinib; however, our analyses were biased because we analyzed retrospectively and did not blind patient clinical information. Prospective analysis is needed to evaluate interstitial shadow by chest CT before treatment with gefitinib.

The Southwest Oncology Group conducted a phase II trial to evaluate gefitinib in patients with advanced bronchioloalveolar carcinoma (SWOG 0126). Previously untreated (n = 102) and treated (n = 36) patients were entered and eligible in SWOG 0126. The response rate was 19% and the median survival time was 12 months in the untreated population.[19] These subset analyses were comparable to our results.

Recently, mutations in the tyrosine kinase domain of EGFR were found to be associated with gefitinib sensitivity in patients with NSCLC.[16,20,21] Our retrospective analyses demonstrated that *EGFR* mutations were detected in four of 13 patients, and those four patients achieved PR in the single agent treatment of gefitinib. These results were compatible with previous reports.[16,20,21]

Thirty patients received second-line chemotherapy, including platinum-based (n = 27) and nonplatinum-based (n = 3) regimens; the response rate was 30%. Pretreatment with gefitinib does not seem to adversely affect the response of second-line chemotherapy. However, our small-scale study does not suggest the best second-line regimen. Platinum combined with any third-generation agents including paclitaxel, docetaxel, vinorelbine,

Table 6. Mutation Status of the *EGFR* Gene

Sex	Age (years)	Pathologic Type	Smoking Status	Overall Survival (months)	*EGFR* Gene	Effect of Mutation	Response to Gefitinib	Response to Second Line Chemotherapy
M	68	AD	Current	14.9	Deletion of 15 nucleotides (2236-2250)	In-frame deletion (E746-A750)	PR	PD
F	67	AD	Current	16.2	Deletion of 15 nucleotides (2236-2250)	In-frame deletion (E746-A750)	PR	PD
F	54	AD	Current	5.6	Deletion of 18 nucleotides (2238-2255) and substitution of T for A at nucleotides 2237	In-frame deletion (L747-S752) and amino acid substitution (F746V)	PR	NR
F	57	AD	Never	25.4	Substitution of G for T at nucleotide 2573	Amino acid substitution (L858R)	PR	SD
M	61	AD	Current	7.5	Wild	—	SD	SD
M	54	AD	Current	9.7	Wild	—	SD	SD
M	45	AD	Current	16.2	Wild	—	SD	PR
M	59	AD	Current	14.7	Wild	—	SD	PR
M	67	SQ	Current	2.4	Wild	—	SD	NR
M	59	AD	Current	24.9	Wild	—	SD	PR
M	61	AD	Current	2.4	Wild	—	PD	NR
F	61	SQ	Current	3.4	Wild	—	PD	PD
F	61	AD	Current	16.3	Wild	—	PD	PR

Abbreviations: EGFR, epidermal growth factor receptor; M, male; F, female; AD, adenocarcinoma; SQ, squamous cell carcinoma; PR, partial response; SD, stable disease; PD, progressive disease; NR, not received.

gemcitabine, or irinotecan is probably acceptable as the current standard first-line chemotherapy.

First-line single agent with gefitinib is active, but produces unacceptably frequent ILD in the Japanese population. Being female, as well as adenocarcinoma, those who never smoked, and *EGFR* mutation were associated with response to gefitinib. Patients who responded to gefitinib did not experience ILD during gefitinib chemotherapy. Further research via genetics and image analysis is needed to avoid ILD and identify a subgroup of patients that benefit from gefitinib treatment. If this is realized, single agent treatment with gefitinib could be an option as first-line chemotherapy in selected patients with advanced NSCLC. Furthermore, randomized trials are warranted to compare first-line single agent treatment with gefitinib followed by second-line platinum-based chemotherapy with first-line platinum-based chemotherapy followed by second- or third-line gefitinib treatment.

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. Marino P, Pampallona S, Preatoni A, et al: Chemotherapy vs supportive care in advanced non-small-cell lung cancer: Results of a meta-analysis of the literature. Chest 106:861-865, 1994
3. Souquet PJ, Chauvin F, Boissel JP, et al: Polychemotherapy in advanced non small cell lung cancer: A meta-analysis. Lancet 342:19-21, 1993
4. Grilli R, Oxman AD, Julian JA: Chemotherapy for advanced non-small-cell lung cancer: How much benefit is enough? J Clin Oncol 11:1866-1872, 1993
5. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002
6. Kelly K, Crowley J, Bunn PA Jr, et al: Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol 19:3210-3218, 2001
7. Smit EF, van Meerbeeck JP, Lianes P, et al: Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: A phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group–EORTC 08975. J Clin Oncol 21:3909-3917, 2003
8. Gridelli C, Gallo C, Shepherd FA, et al: Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer: A phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 21:3025-3034, 2003
9. Alberola V, Camps C, Provencio M, et al: Cisplatin plus gemcitabine versus a cisplatin-based triplet versus nonplatinum sequential doublets in advanced non-small-cell lung cancer: A Spanish Lung Cancer Group phase III randomized trial. J Clin Oncol 21:3207-3213, 2003
10. Kris MG, Natale RB, Herbst RS, et al: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. JAMA 290:2149-2158, 2003
11. Fukuoka M, Yano S, Giaccone G, et al: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 21:2237-2246, 2003
12. Giaccone G, Herbst RS, Manegold C, et al: Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: A phase III trial–INTACT 1. J Clin Oncol 22:777-784, 2004
13. Herbst RS, Giaccone G, Schiller JH, et al: Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: A phase III trial–INTACT 2. J Clin Oncol 22:785-794, 2004
14. Seto T, Yamamoto N: Interstitial lung disease induced by gefitinib in patients with advanced non-small cell lung cancer: Results of a West Japan Thoracic Oncology Group (WJTOG) epidemiological survey. J Clin Oncol 22:632s, 2004
15. Therasse P, Arbuck SG, Eisenhauer EA, et al: New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst 92:205-216, 2000
16. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004
17. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1-10, 1989
18. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
19. West H, Franklin WA, Gumerlock PH, et al: Gefitinib (ZD1839) therapy for advanced bronchioloalveolar lung cancer (BAC): Southwest Oncology Group (SWOG) study S0126. J Clin Oncol 22:620s, 2004
20. Paez JG, Janne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304:1497-1500, 2004
21. Pao W, Miller V, Zakowski M, et al: EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 101:13306-13311, 2004

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Authors' Disclosures of Potential Conflicts of Interest

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ORIGINAL ARTICLE

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Phase I/II study of weekly docetaxel dose escalation in combination with fixed weekly cisplatin and concurrent thoracic radiotherapy in locally advanced non-small cell lung cancer

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Abstract *Purpose*: We conducted a phase I study to determine the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLT) of weekly docetaxel and cisplatin (DOC/CDDP) with concurrent thoracic radiotherapy (TRT) in patients with unresectable stage III non-small-cell lung cancer (NSCLC). *Materials and methods*: The DOC/CDDP administration schedules consisted of a split schedule (SS) with administration in 3 out of every 4 weeks, and a continuous schedule (CS) with administration every week. TRT was given to a total dose of 60 Gy at 2 Gy per fraction over 6 weeks. *Results*: Twenty-one patients entered the study. The patient characteristics were: PS 0/1/2, 6/13/2; Sq/Ad, 16/5; stage IIIA/IIIB, 4/17. The principal DLT was grade3 esophagitis. The MTD of DOC on the SS and CS in combination with CDDP (25 mg/m2/week) was 25 and 20 mg/m^2/week, respectively. We determined the RD and schedule of DOC/CDDP on the SS to be 20/25 mg/m^2/week. The serum α-1-acid glycoprotein (AAG) concentration values were found to be negatively correlated with the grade of esophagitis. The median survival time was 23.1 months. *Conclusion*: The chemoradiation regimen tested in this study has promising activity and manageable toxicity. The continuous schedule could not be recommended due to excessive toxicity. The main DLT was esophagitis, and it significantly correlated with the plasma AAG concentration.

Keywords Docetaxel · Cisplatin · Chemoradiation · AAG

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, and although surgery offers the best chance of cure and long-term survival, only a small percentage of patients present with resectable disease. In fact, 25–30% of patients with NSCLC present with locally or regionally advanced unresectable tumors. Chest irradiation with modern megavoltage equipment plays a critical role in the treatment of these patients, since it assures good local control of the tumor in most patients. However, the development of distant metastases also affects their prognosis, and the addition of chemotherapy to thoracic radiation therapy (TRT) has been proposed in an attempt to reduce the risk of distant metastases.

Recent studies support the benefit of combined modality therapy in stage III NSCLC. The results of randomized studies that used sequential or concomitant chemotherapy for unresectable non-small cell lung cancer have shown significant differences in survival, local control rates, and distant metastasis rates for chemoradiotherapy over radiotherapy alone [1–5], and a recent meta-analysis of all randomized trials that compared TRT alone with the combined approach showed an unequivocal, although modest, survival advantage when cisplatin-based chemotherapy was added to TRT [6]. Concomitant chemoradiotherapy offers the potential advantage of synergistic interactions for local control

and the added possibility of direct antitumor activity [4, 5]. More recently, there has been accumulating phase III evidence that concomitant chemoradiotherapy probably yields higher response rates and survival in patients with stage III disease [7, 8].

Several novel agents with remarkable radiosensitizing properties have recently been introduced in clinical practice. In preclinical studies the taxanes were found to be potent radiation-enhancers by virtue of their ability to cause cell cycle arrest in the radiosensitive G2/M phase [9, 10]. Preclinical studies further illustrated the taxanes' radiosensitizing effect in tumor-cell lines, with docetaxel exhibiting an effect ten times that of paclitaxel at equimolar concentrations [11]. Four phase I trials of docetaxel and concurrent radiation have been reported [12–15]. Mauer et al. [12] and Koukourakis et al. [14] conducted phase I trials of weekly docetaxel with concurrent thoracic radiotherapy and determined that the maximum-tolerated dose (MTD) of weekly docetaxel was 20–30 mg/m^2 with thoracic radiation. The dose-limiting toxicities (DLTs) were esophagitis and neutropenia. The phase II studies of docetaxel [16, 17] and thoracic radiotherapy have shown an encouraging, high response, but an increased incidence of esophagitis and asthenia was observed.

The use of low daily doses of cisplatin concomitantly with RT seems to be of particular interest, since clear synergism has been demonstrated in vitro [18]. In a European Organization for Research and Treatment of Cancer (EORTC) study, daily administration of cisplatin proved to be more effective than a weekly schedule in potentiating the local tumor control achievable with RT alone, although the difference between the two schedules were not statistically significant [4].

In view of these considerations, we planned this phase I study. The objectives of this study were to determine the MTD, recommended dose (RD) and DLT of cisplatin and docetaxel when given weekly concomitantly with conventional TRT, and evaluate the efficacy of this regimen.

Moreover, since it has reported that serum α-1-acid glycoprotein (AAG) combined with docetaxel extensively [19] and that the AAG levels were significantly associated with time to progression in NSCLC patients and febrile neutropenia [20]. The AAG levels were significantly associated with the toxicity of docetaxel because AAG strongly binds docetaxel in serum. Thus, we examined the relationship between serum AAG level and major toxicities in this regimen.

Patients and methods

Patient eligibility

Previously untreated patients with histologically or cytologically documented inoperable stage IIIA or IIIB NSCLC were eligible for this study. Patients with malignant pleural effusion or any disease that required irradiation of more than half of the hemithorax were ineligible. Other eligibility criteria included: (1) age less than 75, (2) Eastern Cooperative Oncology Group performance status equal to or less than 2, (3) evaluable or measurable disease, (4) no prior therapy, (5) adequate bone marrow function (leukocyte count ≥4,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.5 g/dl), renal function (serum creatinine ≤ 2.0 mg/dl), hepatic function (AST/ALT ≤ 2.5 times upper limit of normal, serum bilirubin ≤ 1.5 mg/dl), and pulmonary function (arterial blood gases PaO2 ≥70 mmHg), (6) absence of active infection, heart failure, or acute myocardial infarction within 3 months before study entry, no serious medical or psychiatric illness. All patients signed an informed consent form that was approved by each of the institutional review boards. Before entry into the study, all patients underwent an evaluation that consisted of a complete history and physical examination, chest X-ray, chest and upper abdomen (to include the liver and adrenals) computed tomography (CT) scan, brain CT or MRI, and a bone scan.

Chemotherapy

The treatment regimens are outlined in Fig. 1. The study was designed to fix the cisplatin dose at 25 mg/m^2/week and escalate docetaxel dose. The docetaxel and cisplatin administration schedules were: split schedule (SS), 3 out of every 4 weeks (day 1, 8, 15, 29, 36, and 43), continuous schedule (CS), weekly (day 1, 8, 15, 22, 29, 36). Docetaxel was administered as an intravenous (IV) infusion over 30 min and followed by cisplatin given as an IV infusion over 30 min. The participating investigators at each institution were allowed to decide the volume of fluid replacement and the antiemetic therapy to be administered, but adequate amounts of parenteral fluid and diuretics were given in order to prevent the renal toxicity of cisplatin. The patients did not receive steroids due to prevention of a hypersensitivity reaction. The starting dose of docetaxel was 20 mg/m^2/week, and the docetaxel dose was increased by 5 mg/m^2/week. There was no dose escalation in individual patients, and administration of cisplatin and docetaxel was cancelled if the leukocyte count fell below 2,000/mm^3 or any DLTs occurred.

At first, we planed only sequential schedule. However, as we thought that continuous schedule had a stronger radiosensitizing effect compared with sequential schedule, we amended protocol and added continuous schedule. After the MTD and RD of SS had been determined, we treated with CS using the RD of SS.

Thoracic radiation

Thoracic radiation therapy of 60 Gy in 2.0 Gy fractions was given concurrently with weekly docetaxel and

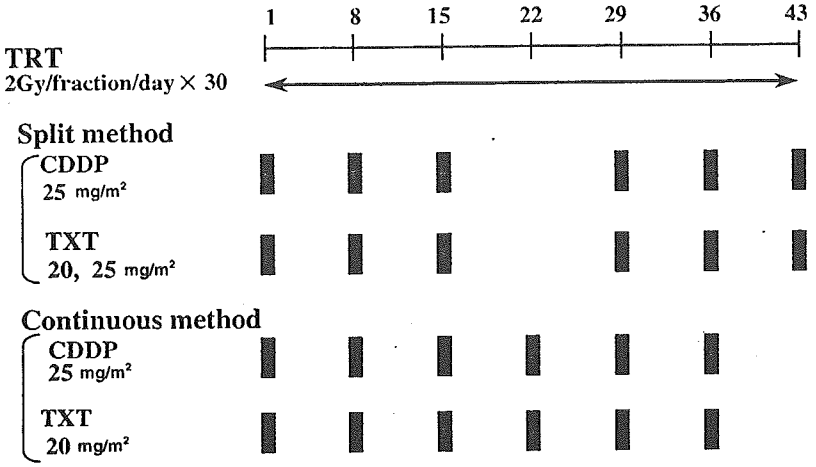

Fig. 1 Treatment regimens for weekly docetaxel and cisplatin concomitant with TRT

cisplatin infusion for 6 weeks. A 6- or 10-MV linear accelerator was used. Two-dimensional treatment planning of TRT was performed by conventional X-ray simulators. Inhomogeneity correction for lung tissues was not done. The initial planning target volume (PTV) consisted of the primary tumor, ipsilateral hilar nodes, and superior mediastinal nodes with 1–1.5 cm margin. If metastasis to supraclavicular nodes were found, they were also included in the initial PTV. This initial large field was treated by parallel-opposed anterior and posterior fields to 40 Gy in 20 fractions. The widths and lengths of the initial fields with appropriate trimming ranged from 10.5 to 16 cm (median; 14 cm) and 10.5–20 cm (median; 16 cm), respectively. After 40 Gy, oblique parallel-opposed fields were used to exclude the spinal cord. The angles of the oblique fields ranged from 15° to 45° with a median of 40°. In the boost fields, the primary tumors and the involved nodes were included with a margin of 0.5–1.5 cm. The total dose to the boost field was 60 Gy in 30 fractions. In the present study, patients were excluded if the initial radiation field exceeded half of the ipsilateral lung. However, no dose constraints on the normal tissues including the percentage of pulmonary volume irradiated to >20 Gy (V20) or esophageal length was determined, as three-dimensional treatment planning using a CT-simulator was not available.

If grade 4 hematologic toxicity occurred during the course of TRT, it was suspended and restarted after recovery to grade 3 or less. If grade 3 or greater esophagitis occurred and the physician decided that the TRT could not be continued, it was suspended and restarted after recovery to grade 2 or less. If PaO_2 fell to 10 torr and a patient had a fever of 38°C or higher, both TRT and chemotherapy were suspended and restarted immediately after recovery.

Definition of MTD, RD and DLT

Maximum-tolerated dose was defined as the dose level at which DLT occurs in more than 50% of the patients treated, and the preceding dose level was defined as RD. At least six patients were entered at each dose level. DLT was defined as grade 4 leukopenia or neutropenia lasting 3 days or more, a platelet count of ≤ 20,000/mm^3, febrile neutropenia and grade 3 or greater non-hematologic toxicities other than nausea and vomiting. Suspension of docetaxel and cisplatin two or more times was also considered as a DLT.

Response evaluation and survival analysis

The criteria for assessing the response to treatment were as follows. Complete response (CR) was defined as total disappearance of all clinically detectable lesions for at least 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the cross-sectional diameters of all measurable lesions for at least 4 weeks, without the development of new lesions. Stable disease (SD) was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, with no clear evidence of either regression or progression for at least 6 weeks. Progressive disease (PD) was defined as an increase of 25% or more 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, together with an increase of assessable disease or the appearance of new lesions. Survival time was defined as the interval between the date of the start of treatment and the date of death due to any cause or the most recent follow-up evaluation. The survival curves were estimated by the Kaplan–Meier method.

Statistical analysis

The *T*-test was used to examine the relationship between serum AAG values and the categorical endpoints of major toxicities, such as grade of esophagitis. A *P*-value of 0.05 or less was considered statistically significant.

Results

Patient characteristics

Between April 1999 and April 2000, 21 patients were enrolled in the study, and their characteristics are listed in Table 1. All patients were eligible for evaluation of efficacy, but one who enrolled at a docetaxel dose of 20 mg/m^2/week in SS was excluded from the evaluation of toxicity because chemotherapy was suspended due to exacerbation of a gastric ulcer. That patient experienced no DLT. The 19 men and 2 women enrolled in the study had a median age of 65 (range: 51–75). Most patients had squamous cell carcinoma ($n=16$: 76%) and stage IIIB disease (n=17: 81%). Median performance status was 1 (range: 0–2), while only two patients had a performance status of 2.

Dose escalation

The DLTs encountered at each dose level are listed in Table 2. On the SS, six and seven patients were evaluable for toxicity at docetaxel doses of 20 and 25 mg/m^2/week, respectively. Two of the six patients at the 20 mg/m^2/week dose experienced DLTs consisting of grade 3 esophagitis in one patient and cancellation of chemotherapy twice because of grade 3 leukopenia in the other. At the 25 mg/m^2/week dose, four of the seven patients developed DLTs consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one, and febrile neutropenia in one. Accordingly, the MTD and RD on the SS were concluded to be a dose of docetaxel 25 and 20 mg/m^2/week, respectively. The next cohort of patients was treated with a docetaxel dose of 20 mg/m^2/week in CS. However, four of the seven patients developed DLTs, consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one patient, and cancellation of chemotherapy twice because of grade 3 neutropenia in one patient. Finally, we concluded that the dose level 1 in SS was the recommended dose for further study of this therapy.

Table 1 Patient characteristics

Characteristic	Number of patients
Total number of patients	21
Assessable for toxicity	20
Assessable for survival and response	21
Age, years	
Median (range)	65 (51–75)
Sex	
Male	19
Female	2
Performance status	
0	6
1	13
2	2
Histology	
Squamous cell carcinoma	16
Adenocarcinoma	5
Stage	
IIIA	4
IIIB	17

Toxicity

Hematologic and non-hematologic toxicities are summarized in Table. 3 and 4. Twenty patients could be assessed for toxicities. The hematologic toxicities were mild, and there were no grade 4 hematologic toxicities. Grade 3 neutropenia, decrease in hemoglobin, and thrombocytopenia were observed in 6 patients (30%), 6 patients (30%), and 1 patient (5%), respectively. Febrile neutropenia developed in only one patient, and it occurred at the 25 mg/m^2/week dose of docetaxel.

The principal toxicity on this regimen was esophagitis. Grade 2 or higher esophagitis occurred in 12 of the 20 (60%) patients enrolled, and in 5 cases (25%) it was of grade 3 and caused suspension of treatment in 2 patients and permanent discontinuation of treatment in one patient at 52 Gy. Another dose-limiting non-hematologic toxicity was grade 3 fatigue which occurred in one patient each at 25 mg/m^2/week dose of docetaxel on the SS and at the 20 mg/m^2/week dose of docetaxel on the CS. Other non-hematologic toxicities were mild and never greater than grade 2. Grade 2 nausea and pneumonitis occurred in five patients and two patients, respectively. No hypersensitivity reactions occurred. There were no treatment related deaths.

Treatment delivery

A total of 110 chemotherapy cycles were administered to 20 patients at three dose levels. Ten (9%) of the planned doses were omitted. The ratio of actual dose intensity to planned dose intensity of docetaxel and cisplatin at 20 and 25 mg/m^2/week docetaxel dose levels on the SS and at the 20 mg/m^2/week docetaxel dose level on the CS was 0.95, 0.93, and 0.88, respectively. A TRT dose of 60 Gy was administered to 18 of 20 (90 %) patients. TRT at the 25 mg/m^2/week dose of docetaxel on the SS and the 20 mg/m^2/week of docetaxel on the CS each one patient was discontinued at 58 and 52 Gy, respectively, because of grade 3 esophagitis.

Response and survival

Table 5 shows the responses observed at each dose level. All 21 patients enrolled were evaluable for response. CR was observed in 5 of the 21 (24%) patients, PR in 14 (67%) and SD in 1 (5%). The overall response rate was 90% (95% confidence interval: 69.6–98.8%). No significant differences in response were observed between the three dose levels of docetaxel.

Table 2 Dose limiting toxicity

Dose of docetaxel	Assessable patients	Dose limiting toxicitiy	
Split schedule			
20 mg/m^2	6	2	1: Grade 3 esophagitis1: 2 times cancellation of chemotherapy due to grade 3 leukopenia
25 mg/m^2	7	4	2: Grade 3 esophagitis1: Grade 3 fatigue1: Febrile neutropenia
Continuous schedule			
20 mg/m^2	7	4	2: Grade 3 esophagitis1: Grade 3 fatigue1: 2 times cancellation of chemotherapy due to grade 3 neutropenia

Table 3 Hematologic toxicity

Dose level of docetaxel	No. of patients	ANC		Febrile neutropenia	Hb		Platelet	
		Grade			Grade		Grade	
		3	4		2	3	2	3
Split schedule								
20 mg/m^2	6	0	0	0	1	2	0	0
25 mg/m^2	7	2	0	1	3	2	1	1
Continuous schedule								
20 mg/m^2	7	4	0	0	2	2	0	0

ANC absolute neutrophil count, *Hb* hemoglobin

Figure 2 shows the overall survival for all 21 patients enrolled in the study; 16 patients (76%) had died at the time of the analysis. All survivors had a follow-up time of 30 months. Based on the Kaplan–Meier method, the 1-, 2-, and 3-year overall estimated survival rates were 71.4, 42.9, and 32.7%, respectively. The median overall survival time was 23.1 months.

Relationship between esophagitis and plasma AAG levels

The principle toxicity on this regimen was esophagitis. Another DLT, grade 3 fatigue occurred in only two patients, and hematologic toxicity was mild. We, therefore, examined the relationship between plasma AAG levels and grade of esophagitis. Plasma AAG was measured in 12 patients prior to the start of the treatment, and the baseline AAG level of the patients who experienced grade 2 or 3 esophagitis was significantly higher ($P=0.04$) than that of the patients who experienced grade 0 or 1 esophagitis (grade 0/1, mean AAG level = 168 pg/ml vs. grade 2/3, mean AAG level = 83 pg/ml: Fig. 3).

Discussion

We conducted a phase I study of cisplatin and docetaxel administered in weekly infusions concomitant with conventional TRT in patients with unresectable stage IIIA/IIIB NSCLC. This is the first study that examined schedule and dose of weekly docetaxel in combination fixed dose of cisplatin 25 mg/m^2 concomitant with TRT. The recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Esophagitis and neutropenia were by far the severest toxicities in this

Table 4 Non-hematologic toxicity

Dose level of docetaxel	No. of patients	Esophagitis		Fatigue		Nausea		Pneumonitis	
		Grade		Grade		Grade		Grade	
		2	3	2	3	2	3	2	3
Split schedule									
20 mg/m^2	6	3	1	0	0	2	0	1	0
25 mg/m^2	7	1	2	0	1	1	0	1	0
Continuous schedule									
20 mg/m^2	7	3	2	1	1	2	0	0	0

Table 5 Response at each dose level

Dose level of docetaxel	No. of patients	Response				Response rate
		CR	PR	SD	PD	
Split schedule						
20 mg/m^2	7	2	5	0	0	7/7100%
25 mg/m^2	7	2	5	0	0	7/7100%
Continuous schedule						
20 mg/m^2	7	1	4	1	0	5/771%
Total	21	5	14	1	1	19/2190%

study, while pulmonary toxicity was almost nonexistent. The pulmonary toxicity associated with concurrent chemoradiotherapy using third generation anticancer agents is frequently serious and fatal. When cisplatin and paclitaxel were combined with concurrent TRT, grade 3 or more late lung toxicity in 20%, including grade 5 in 8% was reported [21]. The incidence of grade 3 or more pulmonary toxicity in the studies of cisplatin and docetaxel concomitant with TRT has been low. Grade 3 pneumonitis occurred in 4.8% of patients in the study by Kiura et al. [22], and no grade 3 or more pulmonary toxicity was reported by Wu et al. [23].

Wu et al. [23] conducted a phase I study of weekly docetaxel and cisplatin concomitant with thoracic radiotherapy in stage III NSCLC and reported that the recommended dose was docetaxel 20 mg/m^2 plus cisplatin 20 mg/m^2 weekly. This dose is almost the same as in our study, but the dose intensity of docetaxel at the recommended dose was slightly lower in our study (docetaxel: 14 mg/m^2/week) than in the Wu study (docetaxel: 20 mg/m^2/week). The reason for this difference may be the dose of cisplatin.

Unfortunately, three-dimensional treatment planning and conformal radiotherapy were not available in the present study. Therefore, it was not possible to analyze a relationship between degree and frequency of toxicities and various dose-volume parameters including V20 or the maximum esophageal point dose. The acute toxicities are closely related to the dose-volume parameters of the normal tissues [24–26]. The degree and frequency of toxicities could be reduced by three-dimensional conformal radiation therapy, which can restrict the dose and volume of the normal tissues compared with conventional two-dimensional technique.

The response rate of 90%, median survival time of 23.1 months, and 2-year survival time of 42.9% obtained in our study are very encouraging. One reason for these favorable results may be that the weekly docetaxel and cisplatin not has only radiosensitizing activity but systemic chemotherapeutic activity. Ohe et al. [27] are currently evaluating docetaxel and cisplatin administered in three consecutive weekly infusions as systemic chemotherapy for advanced NSCLC. Thirty-three elderly patients with advanced NSCLC were enrolled in their phase II study of docetaxel 20 mg/m^2 and cisplatin 25 mg/m^2 on days 1, 8, and 15, doses which are similar to the recommended doses and schedule in our study. The overall response rate was 52%, the complete response rate was 6% and the median survival time was 12.4 months. Both response rate and median survival time in their study are promising and the results suggest that a docetaxel dose of 20 mg/m^2/week plus cisplatin dose of 25 mg/m^2/week has an antitumor effect as systemic chemotherapy.

The correlation with AAG was not a primary objective and this was not essential in this study. Thus, we could collect only 12 samples. The baseline AAG

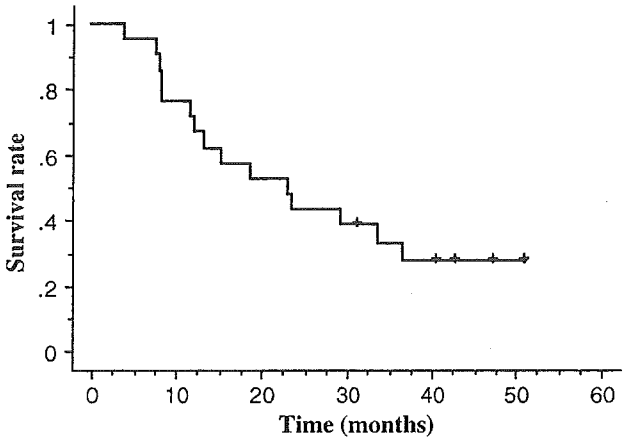

Fig. 2 Overall survival of patients treated with weekly docetaxel and cisplatin concomitant with TRT

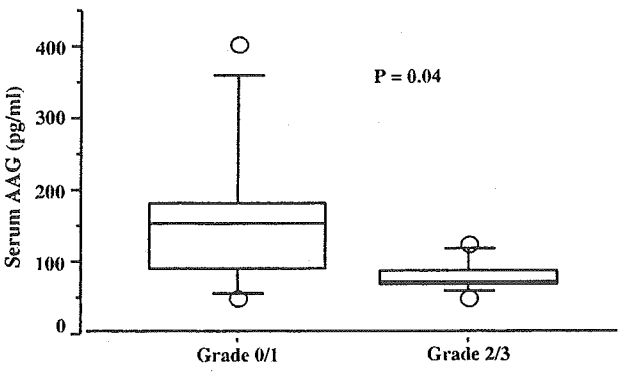

Fig. 3 Relationship between toxicity grade of esophagitis and serum AAG level

levels correlated significantly with the intensity of esophagitis in this study. The plasma AAG level was shown to be a significant predictor of pharmacodynamics in docetaxel treatment of NSCLC by Bruno et al. [20]. Since AAG strongly binds docetaxel, high AAG levels result in a lower free docetaxel fraction, and, therefore, decreased toxicity. The finding that high AAG decreased the grade of esophagitis was not unexpected.

In conclusion, the weekly combination of cisplatin and docetaxel concurrently with TRT is well tolerated and the recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Because of favorable survival and acceptable toxicity profile, we consider this chemoradiotherapy as a warrant for further evaluation in phase II trials.

References

1. Dillman RO, Herndon J, Seagren SL et al (1996) Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 88:1210–1215
2. Le Chevalier T, Arriagada R, Quiox E et al (1991) Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of randomized trial in 353 patients. J Natl Cancer Inst 83:417–423
3. Sause W, Kolesar P, Taylor S et al (2000) Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. Chest 117:358–364
4. Schaake-Koning C, van den Bogaert W, Dalesio M et al (1992) Effects of concurrent cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 326:524–530
5. Jeremic B, Shibamoto Y, Acimovic L et al (1996) Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. J Clin Oncol 14:1065–1070
6. Non-small Cell Lung Cancer Collaborative Group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 311:899–909
7. Furuse K, Fukuoka M, Kawahara M et al (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung caner. J Clin Oncol 17:2692–2699
8. Curran WJ Jr, Scott C, Langer C et al (2000) Phase III comparison of sequential vs concurrent chemoradiation for PTS with unresected stage III non-small cell lung cancer (NSCLC): Initial report of Radiation Therapy Oncology Group (RTOG) 9410. Proc Am Soc Clin Oncol 19:484a
9. Hei TK, Piao CQ, Geard CR et al (1994) Taxol and ionizing radiation: interaction and mechanisms. Int J Radiat Oncol Biol Pys 29(2):267–271
10. Hennequim C, Giocanti N, Favaudon V (1996) Interaction of ionizing radiation with paclitaxel (Taxol) and docetaxel (Taxotere) in HeLa and SQ20B cells. Cancer Res 56(8):1842–1850
11. Choy H, Rodriguez F, Koester S et al (1992) Synergistic effects of toxol/taxotere on radiation sensitivity on human cell lines. Int J Radiat Oncol Biol Phys 24(suppl):274–275
12. Mauer AM, Masters GA, Haraf DJ et al (1998) Phase I study of docetaxel with concomitant thoracic radiation therapy. J Clin Oncol 16:159–164
13. Aamdal S, Wibe E, Hallen MN et al (1997) Phase I study of concomitant docetaxel (Taxotere) and radiation in locally advanced non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 16:460a
14. Koukourakis MI, Kourousis C, Kamilaki M et al (1998) Weekly docetaxel and concomitant boost radiotherapy for non-small cell lung cancer. A phase I/II dose escalation trial. Eur J Cancer 34:838–844
15. Koukourakis MI, Giatromanolaki A, Schiza S et al (1999) Concurrent twice-a-week docetaxel and radiotherapy: a dose escalation trial with immunological toxicity evaluation. Int J Radiat Oncol Biol Phys 43:107–113
16. Aamdal S, Hagen I, Avril I et al (1999) Docetaxel (D, Taxotere) with concurrent radiation in locally advanced non-small cell lung cancer. Proc Am Clin Oncol 18:479a
17. Koukourakis MI, Bahlitzanakis N, Froudarakis M et al (1999) Concurrent conventionally fractionated radiotherapy and weekly docetaxel in the treatment of stage IIIb non-small-cell lung carcinoma. Br J Cancer 80:1792–1796
18. Dewitt L (1987) Combined treatment of radiation and cisdiamminedichloroplatinum (II): a review of experimental and clinical data. Int J Radiat Oncol Biol Phys 13:403–426
19. Urien S, Barre J, Morin C et al (1996) Docetaxel serum protein binding with high affinity to alpha1-acid gylcoprotein. Invest New Drug 14:147–151
20. Bruno R, Hille D, Riva A et al (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16:187–196
21. Robert F, Spencer SA, Childs HA III et al (2002) Concurrent chemoradiation therapy with cisplatin and paclitaxel for locally advanced non-small cell lung cancer: long-term follow-up of a phase I study. Lung Cancer 37(2):189–199
22. Kiura K, Ueoka H, Segawa Y et al (2003) Phase I/II study of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer. Br J Cancer 89:795–802
23. Wu HG, Bang YJ, Choi EK et al (2002) Phase I study of weekly docetaxel and cisplatin concurrent with thoracic radiotherapy in stage III non-small-cell lung cancer. Int J Rad Oncol Biol Phys 52(1):75–80
24. Werner-Wasik M, Pequignot E, Leeper D et al (2000) Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated esophagus: a multivariate analysis of patients with lung cancer treated with nonoperative therapy. Int J Radiat Oncol Biol Phys 48(3):689–696
25. Tsujino K, Hirota S, Endo M et al (2003) Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 55(1):110–115
26. Singh AK, Lockett MA, Bradley JD (2003) Predictors of radiation-induced esophageal toxicity in patients with non-small-cell lung cancer treated with three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 55(2):337–341
27. Niho S, Ohe Y, Yokoyama A et al (2003) A phase II study of docetaxel (D) and cisplatin (C) (DC) administered as three consecutive weekly infusions in elderly patients (pts) with advanced non-small cell lung cancer. Proc Am Soc Clin Oncol 22:679

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Second Primary Cancers in Patients with Stage III Non-Small Cell Lung Cancer Successfully Treated with Chemo-radiotherapy

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Background: Patients successfully treated for non-small cell lung cancer (NSCLC) remain at risk for developing second primary cancer (SPC). The purpose of the current study is to assess the incidence of SPC and the impact of smoking status on the SPC in long-term survivors with stage III NSCLC after chemo-radiotherapy.
Methods: Using the database from the Japan National Hospital Lung Cancer Study Group between 1985 and 1995, information was obtained on 62 patients who were more than 3 years disease-free survivors. Details of clinical information and most smoking history were available from the questionnaire.
Results: Nine of the 62 patients developed SPC 3.9–12.2 years (median, 6.2 years) after the initiation of the treatment. The site of SPC was 2 lung, 1 esophagus, 2 stomach, 1 colon, 1 breast, 1 skin and 1 leukemia. Among these nine, three cancers occurred inside the radiation field. The relative risk of any SPC was 2.8 [95% confidence interval (CI) 1.3–5.3]. The risk changed with the passage of time and it increased significantly (5.2 times at or beyond 7 years) after the treatment. In univariate analysis, the patients who were male, had more cumulative smoking and continued smoking, had an increased risk of SPC [relative risk (RR) 2.7, CI 1.1–5.3; RR 3.0, CI 1.2–6.2; RR 5.2, CI 1.6–11.7, respectively]. In multivariate analysis, factors including smoking status and histological type had no effect on the development of a SPC.
Conclusion: The patients with stage III NSCLC successfully treated with chemo-radiotherapy were at risk for developing SPC and this risk increased with time.

Key words: second primary cancer – non-small cell lung cancer – chemo-radiotherapy

INTRODUCTION

The introduction of combined modality therapy as chest radiotherapy (RT) and chemotherapy for patients with stage III non-small cell lung cancer (NSCLC) has resulted in achieving ~15% long time survivors (123). However, patients successfully treated for NSCLC as well as small cell lung cancer (SCLC) remain at risk for developing second primary cancer (SPC) (4). The risk of SPC in patients with NSCLC has been studied mainly in cohorts of surgically resected patients for stage I NSCLC (567). These reports suggest that the risk of developing SPC and second primary lung cancer (SPLC) is 1–4% and 1–2% per patient per year, respectively, and it appears to increase with the passage of time. Another study including stages I and II patients treated with chest RT confirmed a similar trend that the risk of developing SPC and SPLC is 4.3 and 1.4% per patient per year, respectively (8). Unlike the studies of the patients with SCLC (9–11), these did not provide adequate follow-up information to determine relative risk. Also, there has been no report to date to evaluate the risk of SPC associated with the treatment of RT with chemotherapy as well as smoking status in stage III NSCLC patients.

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PATIENTS AND METHODS

Information was obtained on 1643 patients with stage III NSCLC between 1985 and 1995, using the database from the National Hospital Study Group for Lung Cancer, including

National Hospital Organization Kinki-chuo Chest Medical Center, National Hospital Organization Toneyama Hospital and National Hospital Organization Okinawa Hospital. Among them, 547 patients were treated with chemo-radiotherapy with or without surgery. Of the 547, the 62 patients were more than 3 years disease-free survivors. The patients who relapsed within the 3 years were excluded in this study. Details of clinical information after the treatment and smoking history of the patients were obtained by a questionnaire, which was completed by directly interviewing the patients or the relatives of deceased patients, or by checking the patient's medical records.

Smoking cessation was defined as completely stopping smoking within 6 months after initiation of treatment. Smoking-related cancers include cancer of the lung, larynx and oral cavity, including pharynx, esophagus, pancreas, bladder, kidney, stomach and uterine cervix. A second primary lung cancer was diagnosed according to the criteria provided by Martini and Melamed in 1975 (12). The period of the study was taken as starting from the first day of therapy, and the date of second cancer was taken as the day of histological or cytological documentation of cancer.

For estimation of the expected values of SPC development, the period of risk began 3 years after initiation of treatment and ended with the date of death, date of last follow-up or date of diagnosis of a SPC, whichever occurred first. Age, gender and period-specific rates for cancer incidence within the period 1985–98 obtained from the Research Group for Population-based Cancer Registration in Japan were applied to the appropriate person-years of observation (13). Statistical methods for risk estimation were based on the assumption that observed number of second cancers followed a Poisson distribution (14). To calculate excess risks per 10 000 patients per year in subgroups with significant relative risks, the expected number of cases was subtracted from the number observed. The difference was divided by person-years of observation, and multiplied by 10 000. The risk of a SPC with a specific exposure as smoking was estimated by comparing the patients without the specific exposure, using Poisson regression methods adjusting for gender, histology (squamous cell carcinoma versus non-squamous cell carcinoma) and cumulative smoking amount before the treatment of NSCLC (40 pack-years > versus ≥40 pack-years) (15).

RESULTS

The 62 questionnaires completed for each patient showed that none of the patients had past history of cancer of any site nor received previous chemotherapy or RT. The patient characteristics are summarized in Table 1. The end of observation to count the person-years was 31 December 1998. The median follow-up from initiation of therapy was 6.2 years (range 3.1–12.2 years). Of the 62 patients, nine developed SPC in 435 person-years of follow-up. Forty-six patients have remained free of cancer since initial treatment. Three other patients relapsed with NSCLC and still remain alive

Table 1. Patient characteristics (n = 62)

Gender	
Male	50
Female	12
Age (median, range)	61, 34–80
Histology	
Squamous cell carcinoma	30
Adenocarcinoma	21
Large cell carcinoma	10
Adenosquamous carcinoma	1
Stage	
IIIA	32
IIIB	30
Surgery	
Yes	24
No	38
Smoking (median, range)	40 pack-years, 0–120
Stop smoking	
Yes	29
No	16
Unknown	17

receiving second line chemotherapy. Of the 62 patients, 13 have died: 5 from recurrent NSCLC, 4 from SPC, 4 from other causes. Regarding chemotherapy for initial treatment, 39 patients were treated with cisplatin (CDDP) + mitomycin (MMC) + vindesine (VDS), 16 with CDDP + VDS, 4 with carboplatin, 2 with CDDP + irinotecan, with 1 with CDDP + MMC + inorelbine. In the treatment of RT, 66 Gy were given to 5 patients, 60 Gy to10, 56 Gy to 28, 50 Gy to 15 and 40 Gy to 4. Of the 62 patients, surgery was performed in 24 patients after the chemo-radiotherapy.

For smoking status, information was obtained for all the 62 patients before the treatment, but was available for 45 patients after the treatment. Of the 45 patients treated in the analysis, 16 patients continue to smoke and 19 patients stopped smoking. For assessment, 10 never smokers were also added to the 19 stopped patients, and the 29 patients were categorized to the stop smoking group.

Details of nine patients who developed SPC out of the 62 patients are shown in Table 2. There has been no SPC among the ten never smokers. Two patients (cases 5 and 9) developed a SPLC in different lobes from the original NSCLC. Both tumors arose from the ipsilateral side and both patients continued to smoke after the treatment. One of the two lung cancers developed inside the radiation field. The other malignancies consisted of carcinoma of the esophagus, stomach, colon, skin, breast and acute myelogenous leukemia. Two SPC with skin and breast cancer (cases 6 and 8) also developed inside the radiation field.

Table 3 shows the relative and absolute risks of SPC after initiation of therapy for NSCLC. The risk for development of any SPC increased significantly to 2.8 [95% confidence interval (CI) 1.3–5.3]. In spite of the overall increase in risk, there was no significant increase in relative risk of developing a particular cancer. When smoking-related cancers are combined, there was still no significant increased relative risk in the development of SPC.

Table 2. Characteristics of nine patients with second primary cancers

Patient	Age	Gender	CFI (years)	P His	SPT/His	
1	70	M	3.9	LA	Stomach/AD	
2	69	M	11.5	AD	Colon/AD	
3	61	M	6.3	SQ	Esophagus/SQ	
4	65	M	4.5	SQ	Stomach/AD	
5	62	M	5.6	SQ	Lung/SQ	
6	58	M	4.5	AD	Skin/SQ	inside RT field
7	66	M	8.1	SQ	AML	
8	54	F	10.4	LA	Breast/AD	inside RT field
9	66	M	7.9	AD, SQ	Lung/Undiff	inside RT field

CFI, cancer-free interval; P, Primary; His, Histology; AD, adenocarcinoma; LA, large cell carcinoma; SQ, squamous cell carcinoma; Undiff, undifferentiated carcinoma; AML, Acute myeloid leukemia; RT, radiotherapy.

Table 3. Risk of second primary cancers

Site	Obs	E	O/E	95% CI	Absolute risk*
All cancers	9	3.23	2.8	1.3–5.3	238.9
Esophagus	1	0.12	8.6	0.1–47.7	
Stomach	2	0.81	2.5	0.3–8.9	
Colon	1	0.39	2.5	0.1–14.1	
Lung	2	0.50	4.0	0.4–7.2	
Skin	1	0.03	36.2	0.4–201.3	
Breast	1	0.03	36.7	0.4–204.1	
Leukemia	1	0.03	30.9	0.4–171.5	
Smoking-related	5	1.81	2.8	0.9–6.4	

Obs, observed; E, expected.
*Excess risk per 10 000 persons per year.

Next, the effect of the passage of time was evaluated. The relative risk for 3–4 years after the treatment was 2.2 (95% CI 0.1–23.9) and 1.8 (95% CI 0.1–23.9) for 5–6 years, and 5.2 (95% CI 1.4–13.2) for at or beyond 7 years. The risk changed with the passage of time and it increased significantly (5.2 times at or beyond 7 years) after the treatment. The absolute risk was 600.1 per 10 000 persons per years.

Table 4 shows the results of univariate analysis on the relative risk for a SPC. The risk was significant but modestly increased relative to the general population in male and more cumulative smoking amount (2.7 times; 95% CI 1.1–5.3 and 3 times; 95% CI 1.2–6.2, respectively). Among those who continued to smoke, there was a significantly increased relative risk (5.2 times; 95% CI 1.6–11.7). In contrast, those who stopped smoking showed only a 1.8-fold increase (95% CI 0.3–5.9), which was not significantly different from the general population.

Finally, we assessed multivariate analysis and examined the relationship between continued smoking habits and the risk of a SPC, adjusted for gender, histology type and cumulative smoking amount. The results are shown in Table 5. We could not demonstrate that factors such as continued smoking habits, gender, histology type and cumulative smoking amount had effect on the development of a SPC.

Table 4. Risk of second primary cancers by histology, gender and smoking status

	Obs	O/E	95% CI	Absolute risk*
Histology				
SQ	4	2.7	0.7–6.9	
Non-SQ	5	2.6	0.9–6.7	
Gender				
Male	8	2.7	1.1–5.3	246.7
Female	1	4.3	0.1–23.9	
Surgery				
Yes	4	3.6	0.9–9.2	
No	5	2.3	0.7–5.4	
Smoking				
≤40 pack-years	2	2.2	0.2–8.0	
≥40 pack-years	7	3.0	1.2–6.2	324.2
Intercurrent smoking				
Yes	3	1.8	0.3–5.9	
No	5	5.2	1.6–11.7	430.5

SQ, squamous cell carcinoma; Obs, observed.
*Excess risk per 10 000 persons per year.

Table 5. Relative risk of second primary cancers estimated by multivariate analysis

Risk factor	Relative risk	95% CI
Cumulative smoking (<40 pack-years/≥40 pack-years)	1.4	0.2–8.4
Intercurrent smoking (yes/no)	2.3	0.5–10.8
Histology (SQ/non-SQ)	3.3	0.2–3.3
Gender (male/female)	1.0	0.1–11.2

SQ, squamous cell carcinoma.

DISCUSSION

There has been a large body of work that evaluated the risk of SPC in the patients with NSCLC in the treatment of surgery or RT alone (5678). Although the number of survivors in patients with stage III NSCLC has increased by combined modality therapy as chemotherapy and RT, there has been no report to date to evaluate the risk of SPC in these patients. Additionally, Ng and co-workers (16) reported that the relative risk of SPC was 6.1 with the combined chemotherapy and RT and 4.0 with the RT alone, showing a significant difference ($P = 0.03$) in the surviving patients in Hodgkin's disease. Given that, we focused on the NSCLC patients treated with chemo-radiotherapy.

In our study, 9 patients out of 62 long-term survivors of stage III NSCLC treated with chemo-radiotherapy had a SPC. The relative risk for any SPC (2.8; 95% CI 1.3–5.3) compared with the general population was significantly increased. Instead of many reports examining the risk, these do not provide adequate follow-up information to determine relative risk in the patients with NSCLC. Most studies only show a percent risk per patient per year (5–8). In the current study, the overall rate of developing SPC is estimated at 2.9% per patient per year, which is in agreement with the rates in most surgical series. Ginsberg and Rubinstein (5) reported that SPC occurrence rate was 1.7% per patient per year on 247 patients operated for T1 N0 NSCLC. Other studies showed the rate of 2.8% by Martini et al. (6) and 2.4–3.6% by Thomas and Rubinstein (7). In the current study, we also confirmed the effect of the passage of time on developing SPC. Thomas and Rubinstein (7) reported that the rate of SPC increased from 2.4% for the first 5 years after surgical resection to 3.6% after the fifth year.

We previously studied the relative risk of SPC in the SCLC patient successfully treated with chemotherapy with or without RT (9). Our results showed a similar trend as previous studies (10,11) and demonstrated that the patient had a significantly increased relative risk of 3.6 (95% CI 2.0–5.9) and that the patients who continued to smoke demonstrated a significantly increased risk for a SPC (4.3, 95% CI 1.1–15.9, $P = 0.03$) compared with those who stopped smoking.

Unlike the results of SCLC patients study, the risk of SPC in NSCLC patients was lower, and the impact of continued smoking on developing SPC in the patients was less significant, but the reason for this observation is not completely understood. According to the case–control study from Japan (17), lung cancer risk reduction due to smoking cessation appeared to be greater in SCLC than squamous cell carcinoma or adenocarcinoma, and SCLC seems to be more smoking-related than NSCLC. However, there have been a couple of germline polymorphism as cytochrome P 450 1A1 (CYP1A1) and glutathione *S*-transferase class mu (GSTM1), reported, which is implicated in smoking-related carcinogenesis (18,19). Therefore, SCLC patients are speculated to have a higher potential to develop a SPC, particularly smoking-related cancers.

Among NSCLC patients, there seems to be a special group of roentgenographically occult early stage squamous cell carcinoma of the lung. In this patient group, the rate of occurrence of SPC, particularly SPLC was estimated at 3–4% per patient per year (20,21). The risk for SPLC seemed to be substantially higher than that of 1–2% in the NSCLC patients treated with surgery or RT from the previous study and treated with chemo-radiotherapy from our study. Therefore, the group should be given a special focus and be divided from the general population of NSCLC patients in the research of risk of SPC. Most of the patients can be cured by surgery, photodynamic therapy, brachytherapy and chest RT because of its early clinical stage (22), and are not included in our study. Roentgenographically occult early stage squamous cell carcinoma of the lung is associated with the concept of field cancerization (23), and smoking status seems to be very important to evaluate the risk of SPC, which awaits further examination.

A relatively small sample size and rare events such as SPC in this study resulted in large confidence intervals for the estimates. It is still difficult to conclude the effect of continued smoking on the development of SPC. Cigarette smoking causes not only developing cancers but also cardiovascular and lung damage as well (24,25). It may be speculated that continued smokers died off early when interpreting the results. The cessation of smoking is still warranted among patients with stage III NSCLC treated by chemo-radiotherapy.

In conclusion, stage III NSCLC patients treated with chemo-radiotherapy were at risk of developing SPC and this risk increased with time. A large sample size study in a longer follow-up period may be required in further research to conclude the effect of continued smoking on the development of SPC. SPC in another particular group such as roentgenographically occult early stage squamous cell carcinoma of bronchus also awaits further studies.

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References

1. Ohe Y, Ishizuka N, Tamura T, Sekine I, Nishiwaki Y, Saijo N. Japan Clinical Oncology Group. Long-term follow-up of patients with unresectable locally advanced non-small cell lung cancer treated with chemoradiotherapy: a retrospective analysis of the data from the Japan Clinical Oncology Group trials (JCOG0003A). *Cancer Sci* 2003;94:729–34.
2. Komaki R, Seiferheld W, Ettinger D, Lee JS, Movsas B, Sause W. Randomized phase II chemotherapy and radiotherapy trial for patients with locally advanced inoperable non-small-cell lung cancer: long-term follow-up of RTOG 92-04. *Int J Radiat Oncol Biol Phys* 2002;53:548–57.
3. Jeremic B, Shibamoto Y, Acimovic L, Milicic B, Milisavljevic S, Nikolic N, et al. Hyperfractionated radiation therapy and concurrent low-dose, daily carboplatin/etoposide with or without weekend carboplatin/etoposide chemotherapy in stage III non-small-cell lung cancer: a randomized trial. *Int J Radiat Oncol Biol Phys* 2001;50:19–25.
4. Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. *J Natl Cancer Inst* 1998;90:1335–45.
5. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995;60:615–22.
6. Martini N, Bains MS, Burt ME, Zakowski MF, McCormack P, Rusch VW, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg* 1995;109:120–9.
7. Thomas PA Jr, Rubinstein L. Malignant disease appearing late after operation for T1 N0 non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 1993;106:1053–8.
8. Jeremic B, Shibamoto Y, Acimovic L, Nikolic N, Dagovic A, Aleksandrovic J, et al. Second cancers occurring in patients with early stage non-small-cell lung cancer treated with chest radiation therapy alone. *J Clin Oncol* 2001;19:1056–63.