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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EKB-569, a new irreversible epidermal growth factor receptor tyrosine kinase inhibitor, with clinical activity in patients with non-small cell lung cancer with acquired resistance to gefitinib

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Summary EKB-569 is a potent, low molecular weight, selective, and irreversible inhibitor of epidermal growth factor receptor (EGFR) that is being developed as an anticancer agent. A phase 1, dose-escalation study was conducted in Japanese patients. EKB-569 was administered orally, once daily, in 28-day cycles, to patients with advanced-stage malignancies known to overexpress EGFR. Two patients with advanced non-small cell lung cancer with EGFR mutations and acquired gefitinib resistance from the phase 1 study are described in detail. *Case #1* is a 63-year-old man with smoking history. He received treatment from 4 March 2004. Because he had no severe adverse events, a total of 10 courses of therapy were completed through December 16. Grade 2 skin rash and ALT elevation, and grade 1 diarrhea and nail changes developed. A chest CT scan on 4 August 2003 revealed multiple pulmonary metastases that had decreased in size. *Case #2* is a 49-year-old woman with no smoking history. She received therapy from 9 February 2004. She received a total of five courses of the therapy until 22 June 2004. Grade 3 nausea and vomiting

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and grade 1 diarrhea and dry skin developed. A chest CT scan on March 3 revealed multiple pulmonary metastases that had decreased in size. A brain MRI on March 4 showed that multiple brain metastases also had decreased in size. Based on RECIST criteria, they had stable disease but radiographic tumor regression was observed.

1. Introduction

1.1. Efficacy of gefitinib

The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apotosis, angiogenesis, and metastatic spread [1]. EGFR-tyrosine kinase has become a particularly promising drug targeting for treating non-small cell lung cancer. Gefitinib is an orally active, selective EGFR tyrosine kinase inhibitor that blocks signal transduction pathways implicated in proliferation and survival of cancer cells [2]. Responsiveness characteristics include distinct subgroups of women, patients who have never smoked, patients with adenocarcinoma, and Asians [3–5]. Molecular predictive markers have also been investigated. It is suggested that MAPK is a predictive marker for survival after treatment with gefitinib in chemo-naive patients with bronchioloalveolar carcinoma [6]. Patients with P-Akt-positive tumors who received gefitinib had a better response rate, disease control rate, and time to progression than patients with P-Akt-negative tumors, suggesting that gefitinib may be most effective in patients with basal Akt activation [7]. However, it was not possible to predict gefitinib sensitivity by the level of EGFR overexpression as determined by immunohistochemistry [8] or immunoblotting [9]. Recently it has been reported that somatic mutations in the tyrosine kinase domain of the *EGFR* gene occur in a subset of patients with lung cancer who showed a dramatic response to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib [10–12]. All of these mutations were within exons 18 through 21 of the kinase domain of the *EGFR* gene.

1.2. Drug summary

EKB-569 (Wyeth Research, Collegeville, PA) is a potent, low molecular weight, selective, and irreversible inhibitor of EGFR that is being developed as an anticancer agent. EGFR is a receptor tyrosine kinase that is activated by a variety of growth factors. Upon binding ligands, including epidermal growth factor (EGF) or transforming growth factor alpha (TGF-α), EGFR dimerizes and its intracellular kinase domain is activated, leading to the recruitment and phosphorylation of a number of proteins that ultimately lead to cell growth [13,14]. Several features of EKB-569 may provide certain advantages over other EGFR inhibitors. First, EKB-569 is an orally available, small-molecule EGFR inhibitor, whereas antibody-targeted EGFR inhibitors require intravenous (IV) administration. Second, EKB-569 is an irreversible inhibitor of EGFR, while other small-molecule EGFR inhibitors bind EGFR reversibly [15].

1.3. Effects in humans (Japanese)

A phase 1, open-label, dose-escalation study to assess the safety, tolerability, and pharmacokinetics of EKB-569 was conducted in Japanese patients. EKB-569 was administered orally, once daily, in 28-day cycles, to patients (pts) with advanced-stage malignancies known to overexpress EGFR. Enrollment and treatment are completed; 15 pts (six men, nine women) were treated with 25 mg (3 pts), 35 mg (8 pts), or 50 mg (4 pts) of EKB-569. Their median age was 62 years (range 47–72); ECOG performance status varied: 0 = 4/15 (26.7%) or 1 = 11/15 (73.3%).

The most frequently occurring tumor types included non-small cell lung (10 pts) and breast (2 pts). The remaining tumors were renal, leiomyosarcoma, and malignant thymoma (1 pt each). The most frequently reported EKB-569-related adverse events were diarrhea (86.7%), rash (53.3%), anorexia (40.0%), and dry skin (40.0%). Dose-limiting toxicities were observed at the 50-mg dose level with grade 4 interstitial lung disease and grade 3 diarrhea, stomatitis, and increased blood calcium levels. Thus, the maximum tolerated dose was 35 mg EKB-569 per day.

1.4. Molecular analysis of lung cancer specimens

We obtained appropriate approval from the institution and written informed consent from the patients for the comprehensive use of tumor samples for molecular and pathologic analyses. Surgically resected tumor samples were obtained retrospectively before the patients received

any systemic treatment. All of these tumors were formalin fixed and paraffin embedded by the Department of Pathology. To minimize non-neoplastic tissue contamination, the tumor portion was first selected and marked on an H&E-stained tissue section slide by a pathologist. Only the tumor portion was dissected from the unstained tissue section and sent for DNA extraction.

DNA was extracted from the paraffin section containing a representative portion of each tumor, using the QIAamp DNA Mini kit (Qiagen, Hilden, Germany). For mutational analysis of the kinase domain of the *EGFR* coding sequence, exons 19, 20, and 21 were amplified with three pairs of primers (exon 19, F: 5′-TCACAATTGCCAGTTAACGTCT-3′-(this is the convention for writing a primer), R: 5#-cagcaaagcagaaactcacatc; exon 20, F: 5#-tgaaact-caagatcgcattcat, R: 5#-catggcaaactcttgctatcc; exon 21, F: 5#-gagcttcttcccatgatgatct, R: 5#-gaaaatgctggctgacctaaag). The PCR conditions were one cycle at 95 °C for 11 min, 46 cycles at 95 °C for 30 s, 60 °C for 30 s, 72 °C for 40 s, followed by one cycle at 72 °C for 7 min. PCR products were diluted and cycle-sequenced using the Big Dye Terminator v3.1/1.1 cycle sequencing kit (Applied Biosystems, Forster City, CA) according to the manufacturer's instructions. Sequencing products were electrophoresed on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems). All sequencing reactions were performed in both forward and reverse directions and chromatograms were reviewed manually and analyzed by BLAST (basic local alignment search tool). High-quality sequence variations found in both directions were scored as candidate mutations.

2. Clinical cases

Two patients from the Japanese phase 1 study are described in detail.

2.1. Case #1

A 63-year-old man with smoking history (BI: 720) who was treated for hyperlipidemia and hypertension showed an abnormal chest X-ray in February 1996. Further examinations including a chest computed tomography (CT) scan and bronchoscopy revealed an adenocarcinoma of the lung, c-T1N0M0, stage Ia, in the right upper lobe. He had undergone a right upper lobectomy with mediastinal lymph node dissection in July 1996 and was proven to have a well-differentiated adenocarcinoma, p-T1N0M0, stage Ia. After further follow-up, multiple pulmonary metastases in both lungs were found in January 2000. Then he was given first-line chemotherapy of cisplatin and docetaxel beginning in May 2000. After two courses of this regimen, multiple pulmonary metastases had not increased in size by CT scan; however skin metastases were found. He was started on oral gefitinib 250 mg/day on November 2000. After 4 weeks, a CT scan indicated a reduction of multiple pulmonary metastases. During this treatment, grade 2 rash and grade 1 nail changes, AST/ALT elevations, and diarrhea were observed. On June 2002, multiple pulmonary metastases had increased, and this treatment was discontinued. The patient entered a phase I study of a new EGFR tyrosine kinase inhibitor (TAK-165), starting treatment on October 2002. After 2 weeks of treatment, grade 3 anorexia was observed and the therapy was stopped. On February 2003, multiple pulmonary metastases had more increased, and on March 2003, he entered a phase I study of EKB-569, receiving treatment from 4 March 2004. EKB-569 (25 mg) was administered orally, once daily, in 28-day cycles. Because he had no severe adverse events, a total of 10 courses of therapy were completed through December 16. Grade 2 skin rash and ALT elevation, and grade 1 diarrhea and nail changes developed during this therapy. Based on RECIST criteria, the patient had stable disease (SD) but radiographic tumor regression was observed on 4 August 2003 (day 27 in the sixth course) (Fig. 1). The size of multiple pulmonary metastases increase by CT scan on 8 December 2003, and the treatment was stopped on 17 December 2003.

A lung cancer specimen was obtained at surgery and studied by immunohistochemistry. EGFR overexpression was detected. In addition, we found the heterozygous in-frame deletion E746-A750 in exon 19 of the *EGFR* gene by direct sequencing of the specimen.

2.2. Case #2

A 49-year-old woman with no smoking history, who was treated for Basedow's disease, insomnia, and bronchial asthma, had an abnormal chest X-ray in October 2000. Further examinations including a chest CT scan and bronchoscopy revealed lung cancer in the left upper lobe. She was diagnosed with adenocarcinoma, c-T1N0M0, stage Ia. She had a left-upper lobectomy with mediastinal lymph node dissection, which revealed a well-differentiated adenocarcinoma, p-T4N2M1, stage IV. She was then given first-line chemotherapy of carboplatin and paclitaxel beginning in January 2001. After two courses of therapy, she discontinued treatment because of adverse events. Right supraclavicular lymph node metastases were found on August

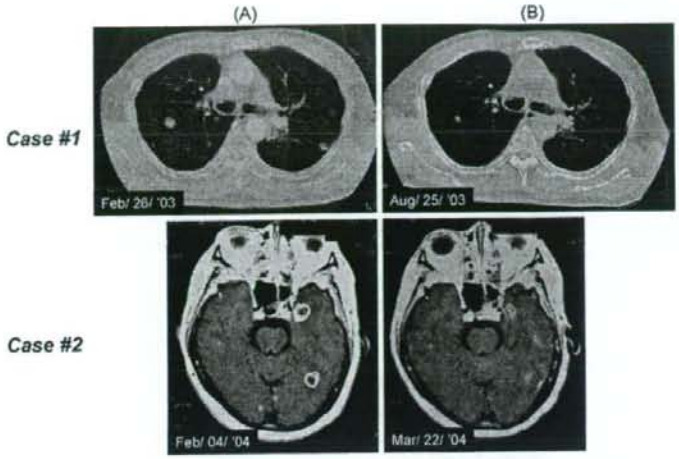

Fig. 1 *Clinical case* #1: a 63-year-old man with adenocarcinoma of lung. CT scan before treatment (A) and after initiation of EKB-569 (B). *Clinical case* #2: a 49-year-old woman with adenocarcinoma of brain metastasis. MRI scan before treatment (A) and after initiation of EKB-569 (B).

2001. Radiotherapy for the metastases (60 Gy/30 fractions) was done, and they decreased in size. On March 2002, right supraclavicular lymph node metastases increased and left clavicular lymph node metastases were found. On April 2002, the patient enrolled in a phase II trial of cisplatin, gemcitabine, and irinotecan for non-small-cell lung cancer. After two courses of therapy, bone metastases were found and pulmonary metastases had grown slowly so the treatment was stopped. She entered a phase I study of a new EGFR tyrosine kinase inhibitor (TAK-165) and started treatment on July 2002. The treatment was stopped after a week later due to grade 3 fatigue. In September 2002, the patient was started on oral gefitinib 250 mg/day. While she was taking 250 mg gefitinib daily for 15 months, the size of multiple pulmonary and bone metastases did not increase by CT scan and she had SD. On December 2003, the patient developed grade 3 oral mucositis and discontinued treatment. On January 2004, the size of multiple pulmonary and bone metastases increase by CT scan. She then entered a phase I study of EKB-569 and received therapy from 9 February 2004. EKB-569 (35 mg) was administered orally, once daily, in 28-day cycles. She received a total of five courses of the therapy until 22 June 2004. Grade 3 nausea and vomiting and grade 1 diarrhea and dry skin developed during the therapy. A chest CT scan on March 3 (day 24 in the first course) revealed multiple pulmonary metastases that had decreased in size. A brain MRI on March 4 (day 25 in the first course) showed that multiple brain metastases also had decreased in size (Fig. 1). The response was SD by RECIST criteria, although tumor regression was observed. The size of bone metastases increase by CT scan on 18 June 2004, and the treatment was stopped on 22 June 2004.

A lung cancer specimen was obtained by surgery and studied by immunohistochemistry. EGFR overexpression was detected. This lung cancer specimen had a heterozygous point mutation in exon 21 (L858R, CTG to CGG) of the *EGFR* gene.

3. Discussion

This is the first case report to describe the effects of EKB-569 on patients with adenocarcinoma of the lung. Case 1 is a 63-year-old man with a smoking history (BI: 720), and case 2 is a 49-year-old woman with no smoking history. Case 1 had an exon 19 deletion of E746-A750, and case 2 had an exon 21-point mutation. These patients underwent surgery and were treated with platinum-based chemotherapy and EGFR tyrosine kinase inhibitors. The treatment with EKB-569 was effective in these two patients after resistance to gefitinib and cytotoxic chemotherapy. These cases suggest that EKB-569 is effective in patients with *EGFR* mutations as has been reported for gefitinib and erlotinib. Despite initial responses to these EGFR inhibitors, patients eventually progress by unknown mechanisms of ''acquired'' resistance.

Recently, a second mutation in the *EGFR* kinase domain, which is associated with acquired resistance of non-small cell lung cancer to gefitinib or erlotinib, was reported [16,17]. Pao et al. showed that in two of five patients with acquired resistance

to gefitinib or erlotinib, progressing tumors contained, in addition to a primary drug-sensitive mutation in EGFR, a secondary mutation in exon 20. This mutation leads to a substitution of methionine for threonine at position 790 (T790M) in the kinase domain [16]. Kobayashi et al. reported the case of a patient with EGFR-mutant, gefitinib-responsive, advanced non-small cell lung cancer who relapsed after two years of complete remission during treatment with gefitinib. The DNA sequence of the EGFR gene in his tumor biopsy specimen at relapse also revealed the presence of the secondary point mutation, T790M [17]. Kurata et al. reported an interesting case in which acquired resistance to gefitinib could be overcome [18]. In this case, the patient received gefitinib, then a combination of nedaplatin and gemcitabine, and then gefitinib again. The cytotoxic agents may have altered the *EGFR* gene or associated genes to produce acquired sensitivity to gefitinib.

Kobayashi et al. also found that CL-387,785, a specific and irreversible, anilinoquinoline EGFR inhibitor [19], strongly inhibited the EGFR kinase in cells transfected with DNA containing the L747-S752 deletion in the *EGFR* gene or a double mutation with the L747-S753 deletion and the T790M point mutation. They speculated that CL-387,785 inhibited the EGFR kinase of the double mutant because of its altered binding to the kinase domain or its covalent binding to EGFR [17]. Kwak et al. used a bronchoalveolar cancer cell line with an L746-A750 deletion in the *EGFR* gene to isolate gefitinib-resistant clones. These clones had not acquired secondary EGFR mutations but were sensitive to the irreversible, anilinoquinoline EGFR inhibitor EKB-569 [20].

We have shown that EKB-569 had clinical activity in two patients with advanced non-small cell lung cancer with EGFR mutations and acquired gefitinib resistance. Thus, irreversible EGFR inhibitors may be an effective therapy for patients with EGFR-mutant advanced non-small cell lung cancer who have relapsed after treatment with gefitinib.

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ORIGINAL REPORT

Phase II Study of Etoposide and Cisplatin With Concurrent Twice-Daily Thoracic Radiotherapy Followed by Irinotecan and Cisplatin in Patients With Limited-Disease Small-Cell Lung Cancer: West Japan Thoracic Oncology Group 9902

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ABSTRACT

Purpose
We initially conducted a randomized phase II study to compare irinotecan and cisplatin (IP) versus irinotecan, cisplatin, and etoposide (IPE) after etoposide and cisplatin (EP) with concurrent twice-daily thoracic radiotherapy (TRT) in limited-disease small-cell lung cancer (LD-SCLC). We amended the protocol to evaluate IP after EP with concurrent twice-daily TRT in a single-arm phase II study because of an unacceptable toxicity in IPE.

Patients and Methods
Previously untreated patients with LD-SCLC were treated intravenously with etoposide 100 mg/m^2 on days 1 through 3 and cisplatin 80 mg/m^2 on day 1 with concurrent twice-daily TRT (1.5 Gy per fraction, a total dose of 45 Gy) beginning on day 2 followed by three cycles of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 of a 4-week cycle.

Results
Of the 51 patients enrolled, 49 patients were assessable for response and toxicity. The overall response rate and complete response rate were 88% and 41%, respectively. The median survival time for all patients was 23 months. The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months. The major toxicities observed were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%), and diarrhea (grade 3 to 4, 14%).

Conclusion
EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be an active regimen which deserves further phase III testing in patients with LD-SCLC.

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INTRODUCTION

Small-cell lung cancer (SCLC), which accounts for approximately 15% of all lung cancer cases, is clinically categorized as the two stages, limited disease and extensive disease. Two meta-analyses have shown the combined modality of chemotherapy and thoracic radiotherapy (TRT) to improve the survival of patients with limited-disease (LD-) SCLC in comparison to chemotherapy alone.[1,2] The schedule, dose, and fractionation of TRT have previously been examined in patients with LD-SCLC in several randomized controlled studies.[3-7] On the basis of the results of these studies, etoposide and cisplatin (EP) with concurrent twice-daily TRT is currently a standard care for the treatment for LD-SCLC. However, the 5-year survival rate is less than 30%, and most patients experience a relapse of the primary tumor or distant metastasis.[3-6] To further improve the therapeutic efficacy, one approach is to develop a new chemoradiotherapy regimen incorporating with a novel active agent.

Irinotecan hydrochloride, a camptothecin derivative, is among the most active chemotherapeutic agents against SCLC with a response rate of 37% as a single agent.[8] A randomized phase III study revealed that irinotecan and cisplatin (IP) was superior to EP in patients with extensive-disease SCLC (ED-SCLC).[9] However, the role of IP in the treatment of LD-SCLC remains to be defined. To clarify the role of this combination regimen in LD-SCLC, we initially conducted a randomized phase II study to

compare two consolidation chemotherapy regimens, IP versus irinotecan, cisplatin and etoposide (IPE), after EP with concurrent twice-daily TRT in LD-SCLC.[10] However, EP with concurrent twice-daily TRT followed by IPE was not feasible because of unacceptable toxicity including grade 4 neutropenia (92%), grade 4 diarrhea (25%), grade 4 infection (25%) and one treatment-related death. We therefore amended the protocol to evaluate EP with concurrent twice-daily TRT followed by consolidation therapy with IP in a single-arm phase II study and herein report the results of this study.

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologically or cytologically confirmed LD-SCLC (stage I disease was excluded) were eligible for this study. A limited stage was defined as disease confined to one hemithorax, the mediastinum, and the bilateral supraclavicular area. Cases with a small amount of pleural effusion and a negative cytology were included in the limited-stage group. Other eligibility criteria included the following: no prior chemotherapy or radiotherapy; measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; age between 20 and 70 years; life expectancy of at least 3 months; adequate baseline organ function defined as leukocyte count ranging from 4,000 to 12,000/mm^3, hemoglobin concentration of at least 9.5 g/dL, platelet count at least 100,000/mm^3, AST and ALT 2.0× the upper limit of the normal range (ULN) or less, serum total bilirubin 1.5 mg/dL or less, serum creatinine ULN or less, 24-hour creatinine clearance of at least 60 mL/min, and Pao_2 at rest of at least 70 mmHg. The radiation portal should be equal or less than half of one lung.

The patients were ineligible if they had the following criteria: interstitial pneumonitis or pulmonary fibrosis; other respiratory diseases that precluded TRT; malignant pleural effusion or malignant pericardial effusion; active concomitant or a recent (< 3 years) history of any malignancy; uncontrolled angina pectoris, myocardial infarction less than 3 months before the enrollment or congestive heart failure; uncontrolled diabetes mellitus or hypertension; severe infection; intestinal paralysis or obstruction; pregnancy or lactation; or other serious concomitant medical conditions. The study protocol was approved by each institutional review board for clinical use. All patients gave their written informed consent before enrollment.

Study Evaluation

The pretreatment baseline evaluation included a complete medical history and physical examination, a CBC, blood chemistry studies, flexible bronchoscopy, electrocardiography, chest radiography, computed tomography of the chest, computed tomography or ultrasound study of the abdomen, computed tomography or magnetic resonance imaging of the brain, bone scintigraphy and bone marrow aspiration with or without biopsy. A CBC and blood chemistry studies were repeated every week. At the end of the study, all of these studies except for flexible bronchoscopy and bone marrow aspiration were repeated unless the patient had stable or progressive disease.

Treatment Schedule

The patients initially received induction chemoradiotherapy consisting of etoposide 100 mg/m^2 on day 1 through 3 and cisplatin 80 mg/m^2 on day 1 with concurrent twice-daily TRT. After the induction chemoradiotherapy, the patients received three cycles of consolidation chemotherapy consisting of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on days 1. Consolidation chemotherapy was repeated every 4 weeks for three cycles.

The first cycle of consolidation chemotherapy was begun 4 week after the initiation of induction chemoradiotherapy if the leukocyte count was at least 4,000/mm^3; the platelet count was at least 100,000/mm^3; AST and ALT 2.0× ULN or less; serum bilirubin 1.5 mg/dL or less; serum creatinine of ULN or less; the patient did not have fever (≥ 38°C), diarrhea within the past 24 hours, or intestinal paralysis or obstruction; and Pao_2 of at least 70 mmHg. The subsequent cycle of consolidation chemotherapy was repeated if the leukocyte count was at least 3,500/mm^3; the platelet count was at least 100,000/mm^3; AST and ALT 2.0× ULN or less; serum bilirubin 1.5 mg/dL or less; serum creatinine ULN or less; the patient did not have fever (≥ 38°C), diarrhea within the past 24 hours, or intestinal paralysis or obstruction. The use of granulocyte colony-stimulating factor (GCSF) was recommended after day 4. However, its administration was withheld on the day of administration of irinotecan.

TRT was performed with 6 MV or higher photons from a linear accelerator and began on day 2 of the induction chemoradiotherapy. Patients received 1.5 Gy per fraction twice daily with at least a 4-hour interval (preferably a 6-hour interval or more) between each fraction over a 3-week period (a total dose of 45 Gy). A radiation field included the primary tumor, the bilateral mediastinal and ipsilateral hilar lymph nodes with a margin of 1.5 to 2.0 cm. Radiation to the supraclavicular lymph nodes was administered only if they were involved. The inferior border extended 5 cm below the carina or to a level including ipsilateral hilar structures, whichever was lower. After initial irradiation with a dose of 30 Gy, off-cord (ie, the spinal cord was outside the field) oblique boost fields were used. The radiation field in the afternoon was not different from that in the morning. Computed tomography planning was not required and lung density corrections were not performed. Prophylactic cranial irradiation (PCI) was administered to the patients achieving complete response or good partial response with a total dose of 25 Gy in 10 fractions.

Dose Modification

Dose modification based on the toxicity of the induction chemoradiotherapy was not allowed at the time of the first administration of IP. In each cycle of IP, irinotecan on day 8 or 15 was withheld if a leukocyte count of less than 2,000/mm^3 or a platelet count of less than 50,000/mm^3 was determined, or if a patient had fever (≥ 38°C) or grade 2 or higher hepatotoxicity or any diarrhea within the last 24 hours or intestinal paralysis or obstruction. In the second and the third cycle of consolidation chemotherapy, the dose modification was made as follows. If a leukocyte nadir count of less than 1,000/mm^3 or a neutrophil nadir count of less than 500/mm^3 for 3 or more days or if febrile neutropenia developed or if a platelet nadir count of less than 25,000/mm^3 was observed or if grade 2 hepatotoxicity or diarrhea was observed, irinotecan was decreased by 10 mg/m^2 in the subsequent cycle, if grade 2 or lower renal toxicity was observed during the previous course of treatment, only cisplatin decreased by 25%, if grade 3 or higher nonhematologic toxicity (excluding nausea, vomiting, and hair loss) developed, then cisplatin decreased by 25% and irinotecan decreased by 10 mg/m^2 in the following cycle. The patients were removed from the study if the following toxicities were observed: grade 4 diarrhea; grade 3 or higher renal toxicity or creatinine of at least 2.0 mg/dL; grade 3 or higher hepatotoxicity; grade 2 or higher pulmonary toxicity or Pao_2 at rest less than 60 mmHg.

Evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for the response assessment.[11] Toxicity was evaluated according to the National Cancer Institute–Common Toxicity Criteria (version 2.0). An extramural review was conducted to validate the eligibility of the patients, staging, and response.

Statistical Analysis

The primary end point of this study was the 2-year survival rate. We calculated the sample size based on Fleming's single-stage design of the phase II study.[12] We set a 2-year survival rate of 35% as a baseline survival rate and 20% as the high level of interest with a power of 0.9 at a one-sided significance level of .05, requiring an accrual of 53 eligible patients. The study was initially begun as a randomized phase II study to compare two consolidation arms, namely IP versus IPE after concurrent chemoradiotherapy. Because of the unacceptable toxicity in the triplet regimen, the study was modified to a single-arm phase II study to evaluate IP after EP with concurrent TRT and 11 patients in the IP arm were included in the analysis of this study.

The duration of survival was measured from the day of entry onto the study, and the overall survival curve and progression-free survival curve were calculated according to the method of Kaplan and Meier.[13]

RESULTS

Patients Characteristics

Between February 2000 and November 2002, 51 patients were enrolled onto this study. Table 1 lists the baseline characteristics of the patients. Two patients were considered to be ineligible because a secondary primary tumor was found after the administration of EP with concurrent TRT. Therefore, 49 patients were assessable for response and toxicity.

Treatment Administration

Seven patients were removed from the study after the administration of EP with concurrent TRT because of treatment delay due to toxicity (six patients) and patient rejection (one patient). Eight patients each discontinued the treatment after each cycle of IP. The major reasons for the discontinuation of IP included treatment delay due to toxicity (three patients), diarrhea (three patients), and ileus (three patients), patient rejection (two patients), and the doctor's judgment (two patients). Overall, 34 patients (69%) received at least two cycles of IP and 26 patients (53%) completed the entire treatment. Irinotecan was omitted in 35 (11%) of 306 cycles. The dose-intensity of irinotecan was 30.5 mg/m^2/wk (68% of the planned dose) and cisplatin 11.6 mg/m^2/wk (77% of the planned dose) in the consolidation chemotherapy.

Response and Survival

On an intention-to-treat basis, the overall response rates and the complete response rates were 88% (95% CI, 78.6% to 96.9%) and 41%, respectively. After a median follow-up of 29.9 months, the median survival time for all patients was 23 months (Fig 1). The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months (Fig 2).

Toxicity

Tables 2 and 3 show the major toxicities. Grade 4 neutropenia was observed in 80% of the patients and 10 (20%) patients had febrile neutropenia in concurrent chemoradiotherapy, whereas grade 4 neutropenia was observed in 40% of the patients and seven patients (17%) had febrile neutropenia in consolidation chemotherapy. In contrast, anemia and thrombocytopenia were relatively mild. One patient had grade 4 esophagitis in concurrent chemoradiotherapy. In the consolidation chemotherapy, grade 3 or 4 diarrhea was observed in six patients (14%) and grade 3 or 4 infection was observed in seven patients (17%). Two patients had grade 3 or 4 radiation pneumonitis. Grade 4 adhesive ileus developed in a patient who had a history of abdominal surgery and ileus. The major toxicities observed through the entire course of the treatment were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%) and diarrhea (grade 3 to 4, 14%). There was one treatment-related death caused by radiation pneumonitis.

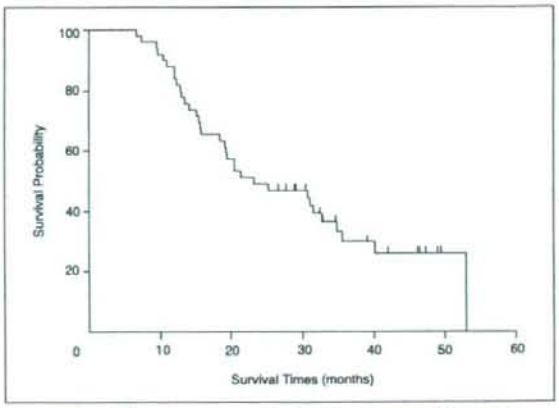

Fig 1. Kaplan-Meier survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median survival time was 23 months, and the 2-year and 3-year survival rates were 49% and 29.7%, respectively.

Patterns of Relapse

Table 4 lists first sites of relapse. Of 12 patients (24%) with local relapse (defined as relapse within the radiation portal), only one had a relapse solely at locoregional sites and 11 at both local and distant site including three with brain metastasis. Of 27 patients (55%) with distant relapse only, 13 had brain metastasis. Overall, 16 patients (33%) showed brain metastasis as the initial site of relapse, and eight of them had received PCI.

Table 1. Patient Characteristics (N = 51)

Characteristic	No.	%
Age, years		
Median	62	
Range	45-70	
Sex		
Male	42	82
Female	9	18
ECOG performance status		
0	22	43
1	28	55
2	1	2
Stage		
II	2	4
IIIA	35	69
IIIB	14	27

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

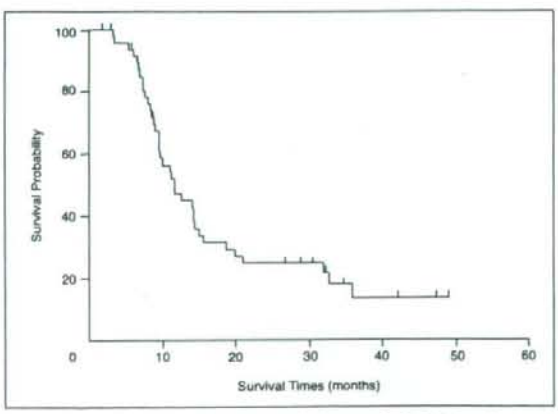

Fig 2. Kaplan-Meier progression-free survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median progression-free survival time was 11.8 months.

Table 2. Major Toxicities During Concurrent Chemoradiotherapy (n = 49)

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Leukopenia	27	55	19	39
Neutropenia	8	16	39	80
Anemia	2	4	1	2
Thrombocytopenia	10	20	0	0
Febrile neutropenia	10	20	0	0
Nonhematologic				
Nausea/vomiting	7	14	0	0
Diarrhea	0	0	0	0
Constipation	0	0	0	0
Infection	9	18	0	0
Mucositis	0	0	0	0
Esophagitis	0	0	1	2
Dyspnea	1	2	0	0
Pneumonitis	0	0	0	0
Hepatic	0	0	0	0
Electrolytes	2	4	2	4

DISCUSSION

In this phase II study, we evaluated the consolidation of IP after EP with concurrent twice-daily TRT and thus achieved an overall response rate of 88%, a 2-year-survival rate of 49% and a 3-year-survival rate of 29.7%. Although the number of assessable patients was slightly smaller than the planned sample size, this study confirmed 24 2-year survivors, and the power calculation showed a 97% probability to correctly reject inactive treatment, thus yielding only a 35% or less 2-year-survival rate. These results are comparable to those in phase III studies evaluating EP with concurrent twice-daily TRT.[3-6] Jeremic et al[7] reported a better survival outcome by using daily carboplatin and etoposide with concurrent twice-daily TRT followed by EP. However, this result has rarely been confirmed by other groups. The Japanese Clinical Oncology Group (JCOG) conducted a pilot study to evaluate the feasibility of IP after EP with concurrent TRT (JCOG9903).[14] The doses and schedule of cisplatin, etoposide, and irinotecan and dose, fractionation and schedule of TRT were similar to ours. They reported that this regimen was feasible with a response rate of 97%, a 2-year survival rate of 41% and a 3-year survival rate of 38%, which are similar to those in our study. Although a phase III study conducted in Japan showed the superiority of IP over EP in ED-SCLC,[9] another phase III study conducted in North America failed to confirm the superiority of IP over EP.[15] A randomized phase III study to compare IP versus EP after EP with concurrent TRT is currently ongoing in patients with LD-SCLC in Japan.

Table 3. Major Toxicities During Consolidation Chemotherapy (n = 42)

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Leukopenia	27	64	8	19
Neutropenia	18	43	17	40
Anemia	17	40	5	12
Thrombocytopenia	8	19	0	0
Febrile neutropenia	7	17	0	0
Nonhematologic				
Nausea/vomiting	9	21	0	0
Diarrhea	5	12	1	2
Constipation	3	7	2	5
Ileus	2	5	1	2
Infection	9	21	1	2
Mucositis	0	0	0	0
Esophagitis	0	0	0	0
Dyspnea	2	5	0	0
Pneumonitis	1	2	1	2
Hepatic	1	2	0	0
Electrolytes	4	10	1	2

Table 4. Site of First Failure (n = 49)

Site	No. of Patients	%
Progression free	10	20
Locoregional	1	2
Locoregional and distant	11	22
Distant	27	55
Brain only	8	16
Brain and others	5	10
Others	14	29

Although a potential approach is to substitute irinotecan for etoposide in the combination of EP with concurrent TRT, we did not combine IP concurrently with TRT because two phase I studies demonstrated that combining IP with concurrent TRT was not feasible when the full dose of irinotecan was administered on days 1, 8, and 15.[16,17] On the basis of these results, we administered IP as consolidation therapy after EP with concurrent twice-daily TRT. After this article was initially submitted, Langer et al[18] reported phase I study of once every 3 weeks scheduling of IP with concurrent twice-daily TRT (45 Gy) or once-daily TRT (70 Gy) in patients with LD-SCLC, thus concluding that IP with concurrent twice-daily TRT was safe and feasible. A further evaluation of this regimen is thus warranted.

One group evaluated IP administered as an induction followed by EP with concurrent twice-daily TRT.[19] Their results are comparable to those of our study and EP with concurrent twice-daily TRT.[3-6] However, this regimen was highly myelotoxic (grade 4 neutropenia, 91%) with febrile neutropenia in 60% of the patients. Furthermore, early TRT is an important issue to obtain the improved outcome in LD-SCLC. Recent meta-analyses revealed that when platinum-based chemotherapy was concurrent with TRT in LD-SCLC, an improved survival was associated with early TRT.[20-22] Another group evaluated the addition of paclitaxel to EP with concurrent TRT.[23] Although their results are comparable to those of our study and EP with concurrent twice-daily TRT,[3-6] they concluded that the triplet regimen would not further improve the survival outcome in patients with LD-SCLC.

Esophagitis is a toxicity of a particular concern in concurrent chemoradiotherapy. We observed grade 3 or 4 esophagitis in one patient (2%), whereas the JCOG9903 trial reported it in 7% of the patients. These figures contrast with those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT (9% to 32%).[3-7] The substitution of irinotecan for etoposide may reduce the incidence of grade 3 or 4 esophagitis. Furthermore, a lower incidence of esophagitis has been noted in a Japanese trial.[4] A possible explanation for this includes differences in the

chemotherapy interval (once every 4 weeks *v* once every 3 weeks) and in ethnic background. Neutropenia was the most prominent toxicity in this study and its incidence is higher than that in the Turrisi et al study.[3] However, no toxic death resulting from neutropenia was observed. Diarrhea was the most troublesome nonhematologic toxicity of irinotecan and one of the major causes for treatment discontinuation in this study.

Brain metastasis as an initial site of relapse was observed in 33% of our patients. The JCOG9903 trial reported brain metastasis in 37% of their patients. These rates were higher than those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT.[4,7] The rate of local recurrence solely was observed in only one patient and none in the JCOG9903 trial. This contrasts with the higher rate of distant failure either with or without local failure in these two studies (77% and 67%, respectively). These increased rates of distant failure including brain metastasis may be partly explained by insufficient administration of IP as consolidation.

A limitation of this study is the treatment feasibility. In this study, 53% of the patients completed the entire treatment and 69% received two or more cycles of IP. The respective values were 58% and 73% in the JCOG9903 trial.[14] In contrast, Takada et al reported that 86% of the patients completed the treatment in EP with concurrent twice-daily TRT.[4] Although the optimal duration of consolidation chemotherapy remains unclear, we consider that at least two cycles of IP is clinically meaningful in view of encouraging survival outcomes in these phase II studies. Whether the relatively low completion rate of IP causes increased distant metastasis and detrimentally affects the outcome will be addressed by the ongoing phase III study. To improve the feasibility, certain supportive measures including the prophylactic GCSF and/or antidiarrheal measures[24] and different dose scheduling (eg, 3-weekly scheduling of IP) should be considered in future studies.

In conclusion, EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be active in patients with LD-SCLC, thus supporting the conduct of the currently ongoing phase III study to compare EP with concurrent twice-daily TRT followed by the consolidation of either EP or IP.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan

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Background: To compare the efficacy and toxicity of three platinum-based combination regimens against cisplatin plus irinotecan (IP) in patients with untreated advanced non-small-cell lung cancer (NSCLC) by a non-inferiority design.
Patients and methods: A total of 602 patients were randomly assigned to one of four regimens: cisplatin 80 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, 15 every 4 weeks (IP) carboplatin AUC 6.0 min × mg/mL (area under the concentration–time curve) on day 1 plus paclitaxel 200 mg/m^2 on day 1 every 3 weeks (TC); cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on days 1, 8 every 3 weeks (GP); and cisplatin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1, 8 every 3 weeks (NP).
Results: The response rate, median survival time, and 1-year survival rate were 31.0%, 13.9 months, 59.2%, respectively, in IP; 32.4%, 12.3 months, 51.0% in TC; 30.1%, 14.0 months, 59.6% in GP; and 33.1%, 11.4 months, 48.3% in NP. No statistically significant differences were found in response rate or overall survival, but the non-inferiority of none of the experimental regimens could be confirmed. All the four regimens were well tolerated.
Conclusion: The four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.
Key words: carboplatin, cisplatin, gemcitabine, irinotecan, non-small-cell lung cancer, paclitaxel, randomized phase III study, vinorelbine

introduction

Nearly 60 000 patients in Japan died of lung cancer in 2004, and the mortality rate is still increasing [1]. Even old-generation cisplatin-based chemotherapy provides a survival benefit and symptom relief in patients with inoperable non-small-cell lung cancer (NSCLC) [2]. Several anticancer agents including irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine, were developed in the 1990s and most of them have mechanisms of action that differ from those of the old-generation agents [3–7]. The combinations of platinum and these new agents developed in the 1990s are more useful against advanced NSCLC than old-generation combination chemotherapy, and doublets of platinum and new-generation anticancer agents are considered standard chemotherapy regimens for advanced NSCLC, although no consistent standard regimens have yet been established [8–17].

Two phase III studies comparing cisplatin plus irinotecan (IP) with cisplatin plus vindesine for advanced NSCLC have been conducted in Japan [18, 19]. Fukuoka et al. [20] reported the results of a combined analysis of the 358 eligible stage IV patients in these studies. They carried out a multivariate analysis using the Cox regression model with adjustment for well-known prognostic factors, and the Cox regression analysis demonstrated that treatment with IP was one of significant independent favorable factor. Based on their data, we selected IP for the reference arm in our study.

The Ministry of Health, Labour and Welfare of Japan approved the prescription of paclitaxel, gemcitabine, and

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vinorelbine for NSCLC in 1999 and requested a phase III study to confirm the efficacy and safety of these agents. The Japanese investigators and the pharmaceutical companies decided to conduct a four-arm randomized phase III study for NSCLC, the so-called FACS, Four-Arm Cooperative Study. The purpose of the study was to compare the efficacy and toxicity of three platinum-based combination regimens, carboplatin plus paclitaxel (TC), cisplatin plus gemcitabine (GP), cisplatin plus vinorelbine (NP), with IP as the reference arm.

patients and methods

patient selection

Patients with histologically and/or cytologically documented NSCLC were eligible for participation in the study. Each patient had to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy, such as malignant pleural effusion, pleural dissemination, malignant pericardiac effusion, or metastatic lesion in the same lobe), at least one target lesion >2 cm, no prior chemotherapy, no prior surgery and/or radiotherapy for the primary site, age 20–74 years, Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, adequate hematological, hepatic and renal functions, partial pressure of arterial oxygen (paO_2) ≥60 torr, expected survival >3 months, able to undergo first course treatment in an inpatient setting, and written informed consent. The study was approved by the Institutional Review Board at each hospital. Written informed consent was obtained from every patient.

treatment schedule

All patients were randomly assigned to one of the four treatment groups by the central registration office by means of the minimization method. Stage, PS, gender, lactate dehydrogenase (LDH) and albumin values, and institution were used as adjustment variables. The first group received the reference treatment, 80 mg/m^2 of cisplatin on day 1 and 60 mg/m^2 of irinotecan on days 1, 8, and 15, and the cycle was repeated every 4 weeks. The second group received 200 mg/m^2 of paclitaxel (Bristol-Myers K.K., Tokyo, Japan) over a 3-h period followed by carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 min × mg/mL on day 1 and the cycle was repeated every 3 weeks. The third group received 80 mg/m^2 of cisplatin on day 1 and 1000 mg/m^2 of gemcitabine (Eli Lilly Japan K.K., Kobe, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. The fourth group received 80 mg/m^2 of cisplatin on day 1 and 25 mg/m^2 of vinorelbine (Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan) on days 1, 8 and the cycle was repeated every 3 weeks. Each treatment was repeated for three or more cycles unless the patient met the criteria for progressive disease or experienced unacceptable toxicity.

response and toxicity evaluation

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors, and tumor markers were excluded from the criteria [21]. Objective tumor response in all responding patients was evaluated by an external review committee with no information on the treatment group. Toxicity grading criteria in National Cancer Institute Common Toxicity Criteria Ver 2.0 were used to evaluate toxicity.

quality of life assessment

Quality of life (QoL) was evaluated by means of the Functional Assessment of Cancer Therapy—Lung (FACT-L) Japanese version and the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoL-ACD), before treatment, immediately before the second cycles of chemotherapy, and 3 and 6 months after the start of treatment [22–24].

statistical analysis and monitoring

The primary end point of this study was overall survival (OS), and the secondary end points were response rate, response duration, time to progressive disease (TTP), time to treatment failure (TTTF), adverse event, and QoL. The 1-year survival rate of the control group in this study was estimated to be 43% based on the data in published papers, and the 1-year survival rate in the other treatment group was expected to be 50%. The lower equivalence limit for 1-year survival rate was set as '−10%'. The criterion for the non-inferiority of each treatment was a lower limit of the two-sided 95% confidence interval (CI) of the 1-year survival rate of treatment minus that of control larger than the lower equivalence limit. Because the non-inferiority of each treatment versus the control was to be evaluated independently, a separate null hypothesis was stated for each treatment, and for that reason no multiple comparison adjustment was included in the study. Based on the above conditions and binomial distribution, 135 patients were needed per arm for a one-sided Type I error of 2.5% and 80.0% power. In view of the possibility of variance inflation due to censoring, the sample size was set at 600 (150 per arm).

Central registration with randomization, monitoring, data collection, and the statistical analyses were independently carried out by a contract research organization (EPS Co., Ltd, Tokyo, Japan).

results

patient characteristics

From October 2000 to June 2002, a total of 602 patients were registered by 44 hospitals in Japan. All patients had been followed up for >2 years, and 447 patients had died as of June 2004. Of the 602 patients registered, 151 were allocated to the reference treatment, IP, and 150, 151, and 150 patients were allocated to TC, GP, and NP, respectively. Since 10 patients did not receive chemotherapy and 11 patients were subsequently found to be ineligible, 592 patients were assessable for toxicity and 581 patients were assessable for efficacy. Four patients did not receive chemotherapy due to electrolytic disorder, fever, symptomatic brain metastases, and rapid tumor progression in IP, two patients due to refusal and pneumonia in TC, four patients due to lower WBC counts (two patients), rapid tumor progression, and nephritic syndrome in NP. Two patents were ineligible due to wrong stage in IP, two patients were wrong stage and one patient had double cancer in TC, two patients were wrong diagnosis, one patient had massive pleural effusion, one patient received prior chemotherapy in GP, one patient had no target lesions in NP. Age, gender, PS, stage, and LDH and albumin values were well balanced in each arm (Table 1). Fewer patients with adenocarcinoma and more patients with squamous cell carcinona were, however, entered in three experimental arms than in IP.

objective tumor response and response duration

Objective tumor response is shown in Table 2. Forty-five partial responses occurred in the 145 assessable patients in the reference arm, IP, for an objective response rate of 31.0% with a median response duration of 4.8 months. The response rate and median response duration were 32.4% and 4.0 months in TC, 30.1% and 3.5 months in GP, and 33.1% and 3.4 months in NP. The response rates in TC, GP, and NP were not statistically different from the rate in IP according to the results of the χ^2 test.

Table 1. Patient characteristics and treatment delivery

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine
Assessable patients	145	145	146	145
Gender (male/female)	97/48	99/46	101/45	101/44
Age, median (range)	62 (30–74)	63 (33–74)	61 (34–74)	61 (28–74)
PS (0/1)	44/101	44/101	45/101	45/100
Histology				
Adenocarcinoma	121	104	108	109
Squamous cell carcinoma	16	31	29	29
Others	8	10	9	7
Stage (IIIB/IV)	31/114	28/117	30/116	26/119
No. of cycles				
Mean ± SD	3.0 ± 1.3	3.5 ± 1.5	3.2 ± 1.2	3.1 ± 1.3
Median	3	3	3	3
Range	1–7	1–10	1–7	1–8

PS, performance status; SD, standard deviation.

Table 2. Survival, TTP, TTTF, response rate, and response duration

	N	Median survival, months	1-year survival (%)	Difference in 1-year survival from IP	2-year survival (%)	TTP (median), months	TTTF (median), months	Response rate (%)	Response duration (median), months
Cisplatin + irinotecan	145	13.9	59.2	–	26.5	4.7	3.3	31.0	4.8 ($n = 45$)
Carboplatin + paclitaxel	145	12.3	51.0	−8.2% (95% CI −19.6% to 3.3%)	25.5	4.5 ($P = 0.355$)[a]	3.2 ($P = 0.282$)[a]	32.4 ($P = 0.801$)[b]	4.0 ($n = 47$)
Cisplatin + gemcitabine	146	14.0	59.6	0.4% (95% CI −10.9% to11.7%)	31.5	4.0 ($P = 0.170$)[a]	3.2 ($P = 0.567$)[a]	30.1 ($P = 0.868$)[b]	3.5 ($n = 44$)
Cisplatin + vinorelbine	145	11.4	48.3	−10.9% (95% CI −22.3% to 0.5%)	21.4	4.1 ($P = 0.133$)[a]	3.0 ($P = 0.091$)[a]	33.1 ($P = 0.706$)[b]	3.4 ($n = 48$)

[a]Compared with IP by the generalized Wilcoxon test.

[b]Compared with IP by the χ^2 test.

CI, confidence interval; IP, cisplatin plus irinotecan; TTP, time to progressive disease; TTTF, time to treatment failure.

OS, TTP disease, and TTTF

OS and TTP are shown in Figure 1. Median survival time (MST), the 1-year, and 2-year survival rate in IP were 13.9 months, 59.2%, and 26.5%, respectively. The MSTs, 1-year, and 2-year survival rates were, respectively, 12.3 months, 51.0%, and 25.5% in TC; 14.0 months, 59.6%, and 31.5% in GP; and 11.4 months, 48.3%, and 21.4% in NP. The lower limits of the 95% CI of the difference in 1-year survival rate between IP and TC (−19.6%), GP (−10.9%), and NP (−22.3%) were below −10%, which was considered the lower equivalence limit (Table 2). Thus, the results did not show non-inferiority in three experimental regimens compared with reference treatment. Median TTP and median TTTF were 4.7 and 3.3 months, respectively in IP. Median TTP and TTTF were, respectively, 4.5 and 3.2 months in TC, 4.0 and 3.2 months in GP, and 4.1 and 3.0 months in NP. There were no statistical differences in either TTP or TTTF in TC, GP, or NP, compared with IP according to the results of the generalized Wilcoxon test (Table 2).

hematologic and non-hematologic toxicity

In IP, 47.6% and 83.7% of patients developed grade 3 or worse leukopenia and neutropenia, respectively (Table 3). The incidences of grade 3 or worse leukopenia (33.1%, $P = 0.010$) and neutropenia (62.9%, $P < 0.001$) were significantly lower in GP than in IP. The incidence of grade 3 or worse leukopenia (67.1%, $P < 0.001$) was significantly higher in NP than in IP. Grade 3 or worse thrombocytopenia developed in 5.4% of the patients in IP, and the incidence was significantly higher in GP (35.1%, $P < 0.001$). The incidence of febril neutropenia in IP was 14.3%, and was significantly lower in GP (2.0%, $P < 0.001$).

Grade 2 or worse nausea, vomiting, anorexia, and fatigue occurred in 60.5%, 51.0%, 65.3%, and 38.8%, respectively, of the patients in IP. The incidences of grade 2 or worse nausea (TC: 25.0%, $P < 0.001$, NP: 47.3%, $P = 0.022$), vomiting (TC: 22.3%, $P < 0.001$, NP: 36.3%, $P = 0.011$), and anorexia (TC: 32.4%, $P < 0.001$, NP: 49.3%, $P = 0.005$) were significantly lower in TC and NP than in IP. Grade 2 or worse diarrhea was

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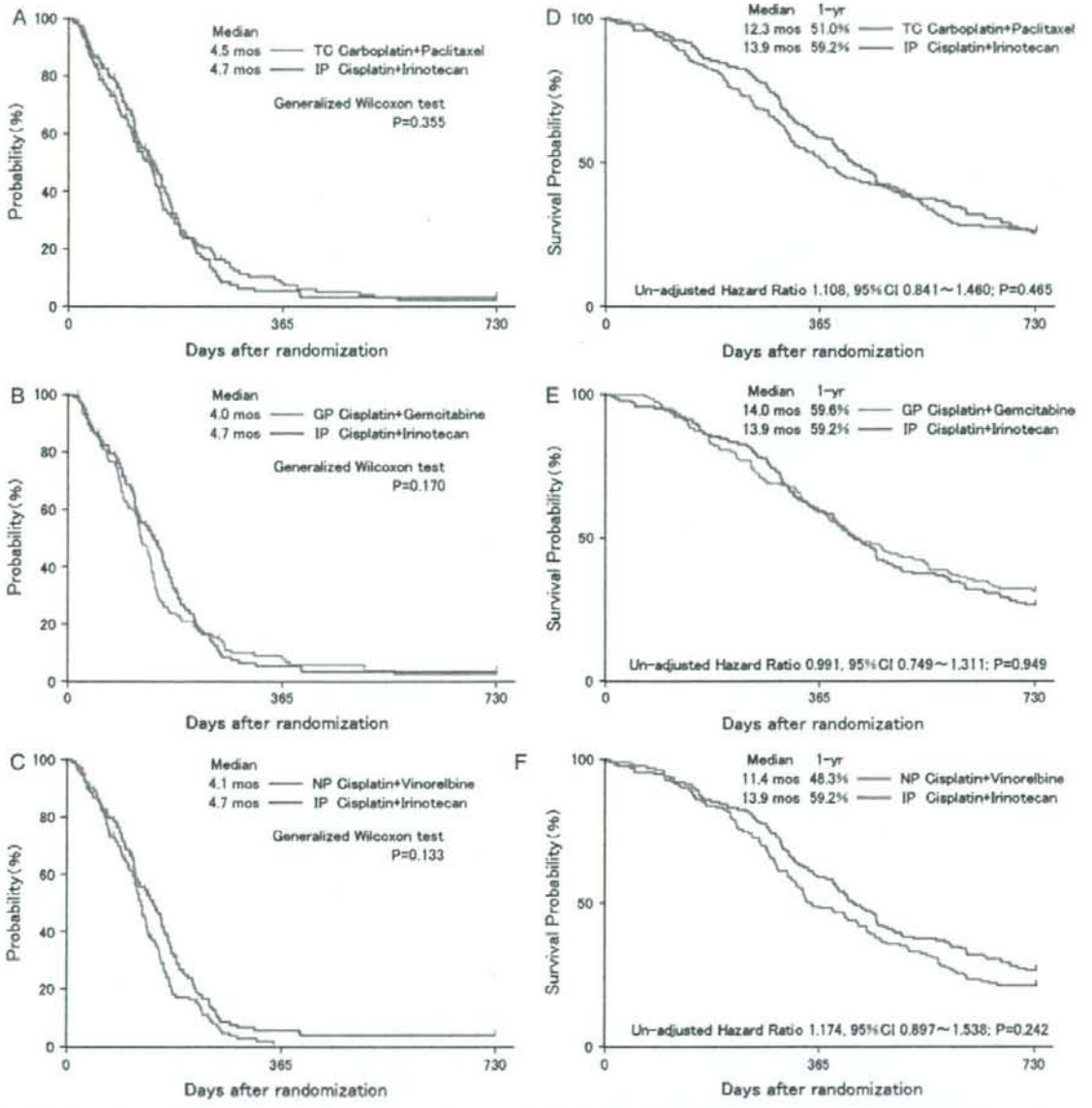

Figure 1. Overall survival (OS) and time to progressive (TTP) disease. TTP and OS in the carboplatin plus paclitaxel (TC) (A, D), cisplatin plus gemcitabine (GP) (B, E), and cisplatin plus vinorelbine (NP) (C, F) were not statistically significantly different from the values in the cisplatin plus irinotecan.

significantly less frequent in TC (6.8%), GP (8.6%), and NP (11.6%) than in IP (48.3%, $P < 0.001$). The incidences of grade 2 or worse sensory neuropathy (16.9%, $P < 0.001$), arthralgia (21.6%, $P < 0.001$), and myalgia (17.6%, $P < 0.001$) were significantly higher in TC than in IP. Grade 2 alopecia occurred in 30.6% of the patients in IP, and its incidence was significantly higher in TC (44.6%, $P = 0.013$) and significantly lower in GP (15.2%, $P = 0.001$) and NP (8.9%, $P < 0.001$). Grade 2 injection site reactions were more frequent in NP (26.7%) than in IP (4.8%, $P < 0.001$).

A total of five patients died of treatment-related toxicity: three in IP (cerebral hemorrhage, interstitial pneumonia, acute circulatory failure/disseminated intravascular coagulation: 2.0%), one in TC (acute renal failure: 0.7%), and one in NP (pulmonary embolism: 0.7%).

second-line treatment

Data on second-line treatment, but not third-line or later treatment, was available in this study, and they showed that

Table 3. Toxicity

	IP (n = 147)			TC (n = 148)			GP (n = 151)			NP (n = 146)		
	Grade (%)			Grade (%)			Grade (%)			Grade (%)		
	2	3	4	2	3	4	2	3	4	2	3	4
Leukocytes	42	43	5	39	42	3	40	31[a]	2[a]	25	51[b]	16[b]
Neutrophils	11	39	45	5	19	69	21	40	23[a]	5	16	72
Hemoglobin	42	24	7	42	13[a]	2[a]	44	22	5	43	25	5
Platelets	6	5	1	9	11	0	22	35[b]	0[b]	3	1[a]	0[a]
Febrile neutropenia	–	14	0	–	18	0	–	2[a]	0[a]	–	18	0
Nausea	32	29	–	14[c]	11[c]	–	35	23	–	33[c]	14[c]	–
Vomiting	38	13	0	17[c]	5[c]	0[c]	34	14	0	29[c]	7[c]	0[c]
Anorexia	30	33	2	15[c]	17[c]	1[c]	31	26	1	29[c]	20c	1[c]
Fatigue	27	12	1	26	2	1	17[c]	3[c]	0[c]	23[c]	3[c]	0[c]
Diarrhea	33	15	1	4[c]	3[c]	0[c]	7[c]	2[c]	0[c]	8[c]	4[c]	0[c]
Constipation	27	7	0	30	8	0	33	9	0	40[d]	14[d]	0[d]
Neuropathy, motor	1	0	0	1	1	1	0	0	0	0	0	0
Neuropathy, sensory	1	0	0	14[d]	3[d]	0[d]	0	0	0	0	0	0
Alopecia	31	–	–	45[d]	–	–	15[c]	–	–	9[c]	–	–
Arthralgia	2	0	0	20[d]	2[d]	0[d]	0	0	0	1	0	0
Myalgia	1	0	0	16[d]	2[d]	0[d]	0	0	0	1	1	0
Injection site reaction	5	0	–	5	0	–	5	0	–	27[d]	0[d]	–
Pneumonitis	0	1	1	0	1	0	0	0	0	0	1	0
Creatinine	8	1	0	2[c]	0[c]	0[c]	7	0	0	8	1	0
AST	7	1	1	5	1	0	6	3	0	1	3	0
Fever	2	0	0	5	1	0	1	0	0	1	0	0
Treatment-related death	3 (2.0%)			1 (0.7%)			0			1 (0.7%)		

[a]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) lower than that with IP.
[b]Incidence of grade 3 or 4 toxicity significantly ($P < 0.05$) higher than that with IP.
[c]Incidence of grade 2 or worse toxicity is significantly ($P < 0.05$) lower than that with IP.
[d]Incidence of grade 2 or worse toxicity significantly ($P < 0.05$) higher than that with IP.
GP, cisplatin plus gemcitabine; IP, cisplatin plus irinotecan; NP, cisplatin plus vinorelbine; TC, carboplatin plus paclitaxel.
AST, aspartate aminotransferase; –, no category in the criteria.

60%–74% of the patients received chemotherapy and 6%–9% received thoracic irradiation as second-line treatment (Table 4). The percentages of patients in each treatment group who received second-line chemotherapy were not significantly different ($P = 0.081$).

quality of life

The details of the QoL analysis will be reported elsewhere. No statistically significant difference in global QoL was observed among the four treatment groups based on either the FACT-L Japanese version or the QoL-ACD. Only the physical domain evaluated by QoL-ACD was significantly better in TC, GP, and NP than in IP.

discussion

Many randomized phase III studies have compared platinum-plus-new-agent doublets in NSCLC, but, this is the first to evaluate the efficacy of an irinotecan-containing regimen in comparison with other platinum-plus-new-agent doublets in NSCLC [14–17]. Although non-platinum-containing chemotherapy regimens are used as alternatives, doublets of platinum and a new-generation anticancer agent, such as TC, GP, and NP, are considered standard chemotherapy regimens for advanced NSCLC worldwide [13–17, 25]. Although the non-inferiority of none of the three experimental regimens could be confirmed in this study, no statistically significant differences in response rate, OS, TTP, or TTTF were observed between the reference regimen and the experimental regimens. All four platinum-based doublets have similar efficacy against advanced NSCLC but different toxicity profiles. Nevertheless, IP was still regarded as the reference regimen in this study because the non-inferiority of none of the three experimental regimens could be confirmed.

OS in this study was relatively longer than previously reported. The estimated 1-year survival rate in the reference arm was 43%, but the actual 1-year survival rate was 59.2%, much higher than expected. The MSTs reported for patients treated with TC, GP, and NP in recent phase III studies have ranged from 8 to 10 months, and in the present study they were 12.3, 14.0, and 11.4 months, respectively [14–17]. One reason for the good OS in this study was the difference in patient selection criteria, for example exclusion of PS2 patients. Ethnic differences in pharmacogenomics have also been indicated as a possible reason for the good OS in this study [26]. The OS in IP in this study, however, was better than in previous Japanese studies [18, 19]. TTP in this study ranged from 4.0 to 4.7 months, and was similar to the TTP of 3.1–5.5 months reported in the literature [15, 16]. OS not TTP was longer in this study

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Table 4. Second-line treatment

	Cisplatin + irinotecan	Carboplatin + paclitaxel	Cisplatin + gemcitabine	Cisplatin + vinorelbine	
Number of patients	145	145	146	145	
Chemotherapy	107 (74%)	87 (60%)	101 (69%)	95 (66%)	$P = 0.081$
Docetaxel	39	25	50	51	
Gefitinib	11	9	18	12	
Paclitaxel	15	14	7	11	
Gemcitabine	24	28	17	28	
Vinorelbine	9	12	2	9	
Irinotecan	15	4	3	3	
Thoracic irradiation	8	10	13	10	

than previously reported, and higher 2-year survival rates, 21.4%–31.5%, were observed in the minimum 2-year follow-up in this study. Second-line or later treatments may affect survival, because docetaxel has been established as standard second-line chemotherapy for advanced NSCLC [27, 28]. Gefitinib is also effective as second-line or later chemotherapy for advanced NSCLC, especially in Asian patients, never smokers and patients with adenocarcinoma [29–32].

The toxicity profile of each treatment differed and the toxicity of all four regimens was well tolerated. Overall QoL was similar in the four platinum-based doublets. Only physical domain QoL evaluated by the QoL-ACD was statistically better in TC, GP, and NP than in IP. This finding is presumably attributable to the fact that diarrhea is a statistically less frequent adverse effect of TC, GP, and NP than of IP.

In conclusion, all four platinum-based doublets had similar efficacy for advanced NSCLC but different toxicity profiles. All the four regimens can be used to treat advanced NSCLC patients in clinical practice.

appendix

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