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Abbreviations: JCOG, Japan Clinical Oncology Group; SCLC, small cell lung cancer; ED, extensive disease; OS, overall survival; WJOG, West Japan Oncology Group; NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; OLCSG, Okayama Lung Cancer Study Group; TCOG, Tokyo Cooperative Oncology Group; NPO, nonprofit organization; NEJSG, North East Japan Study Group; CJLSG, Central Japan Lung Study Group; TORG, Thoracic Oncology Research Group; LOGiK, Lung Oncology Group in Kyushu

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1. Introduction

Lung cancer is the most common cause of death from cancer in Japan, being responsible for more than 70,000 deaths annually. Most individuals with lung cancer are already at an advanced stage of the disease at the time of diagnosis. Chemotherapy is the mainstay of treatment for such patients, but their median survival time is limited to ~15 months [1,2]. The development of new treatment strategies to improve the clinical outcome of individuals with this challenging disease is thus a priority.

The establishment of more effective treatments for advanced lung cancer requires the performance of scientifically and ethically valid prospective multicenter clinical trials. The first professional cooperative study group for lung cancer research in Japan was the Japan Clinical Oncology Group (JCOG), which was formed in 1990. Several other cooperative study groups for lung cancer were subsequently established to promote and support multicenter clinical trials of new treatments for this disease. Recently, the "Study for Enhancement of Quality and Efficiency of Cancer Therapeutic Development Research via Collaboration among Cooperative Groups and Designated Cancer Care Hospitals" was established to enhance collaboration of eight selected Japanese cooperative groups for lung cancer. It is supported by the National and Cancer Research Development Fund (26-A-22) and is chaired by Haruhiko Fukuda and Nobuyuki Yamamoto. For this review, we collected information about eight cooperative study groups by direct interviews. This review describes the current status and future challenges of investigator-initiated clinical trials for lung cancer.

2. Clinical Trial Groups in Japan

2.1. *Japan Clinical Oncology Group*

The Japan Clinical Oncology Group (JCOG) was launched in 1990 as a cooperative study group to perform multicenter clinical trials for cancer in Japan (Fig. 1, Table 1). It remains the only Japanese cooperative group supported primarily by a governmental research fund. Staff at the headquarters of JCOG, which includes a Data Center (director, Haruhiko Fukuda) and an Operations Office (director, Kenichi Nakamura), work closely with individual investigators to support the operational aspects of clinical trials. They thus provide help with protocol development, patient registration, reporting of adverse events, data management, and statistical analysis as well as perform regular (twice a year) central monitoring and site visit audits.

The individual study groups of JCOG are currently divided into 16 categories on the basis of specific tumor type or treatment modality. Among them, the Lung Cancer Study Group (LCSG) consists of 38 institutions distributed throughout the country and has conducted several practice-changing clinical trials, in particular for small cell lung cancer (SCLC). The first chair of LCSG was Nagahiro Saijo (1982–2002), who was succeeded by Tomohide Tamura (2002–2014) and then by Yuichiro Ohe (elected in 2014). One of the landmark trials performed by LCSG was a randomized phase III trial comparing cisplatin plus irinotecan with cisplatin plus etoposide (the standard treatment at the time) in chemotherapy-naïve patients with extensive disease (ED)-stage SCLC (JCOG9511) [3]. The trial was terminated early because the planned interim analysis showed a highly significant improvement in overall survival (OS) for patients treated with cisplatin plus irinotecan compared with those who received cisplatin plus etoposide. Although two subsequent large phase III trials in the United States failed to show a significant difference in OS between these two regimens, cisplatin plus irinotecan is now considered the standard regimen for previously untreated patients with ED-SCLC in Japan.

The number of elderly SCLC patients continues to rise with the growing geriatric population, with ~50% of individuals with SCLC now 70 years of age or older. JCOG performed a phase III trial comparing split doses of cisplatin (25 mg/m^2, days 1–3) plus etoposide (80 mg/m^2, days 1–3) (SPE regimen) with carboplatin (area under the curve=5, day 1) plus etoposide (80 mg/m^2, days 1–3) (CE regimen) in elderly (>70 years of age) or high-risk patients with ED-SCLC (JCOG9702) [4]. Although thrombocytopenia of grade 3 or 4 occurred more frequently in the CE arm than in the SPE arm (56% versus 14%, $P<0.01$), both regimens were found to be feasible and active, yielding a median OS of ~10 months. On the basis of the results of this phase III study, the CE regimen is now commonly used for elderly untreated patients with ED-SCLC. JCOG has recently initiated a randomized phase III trial comparing carboplatin plus irinotecan with the CE regimen for elderly (≥70 years) chemotherapy-naïve patients with ED-SCLC (JCOG1201) (Fig. 2A).

2.2. *West Japan Oncology Group*

The West Japan Thoracic Oncology Group (WJTOG) was established in 1992 as an expert group specific for lung cancer (Table 1). It was initially named the West Japan Lung Cancer Study Group, and it subsequently became the West Japan Oncology Group (WJOG) after joining gastrointestinal and breast

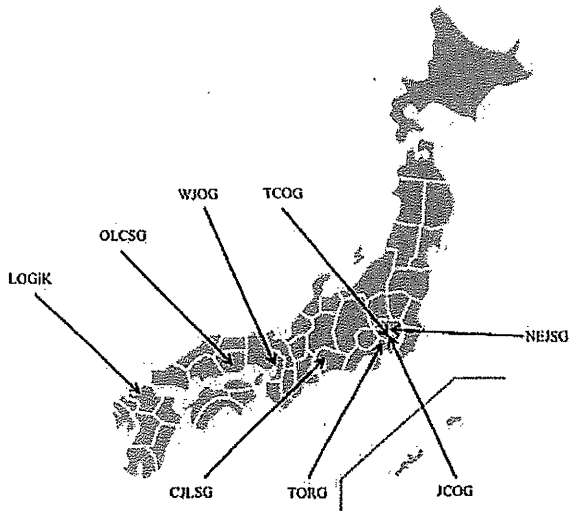

Fig. 1 – Cooperative study groups for lung cancer in Japan.

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Table 1 – Characteristics of the clinical study groups for lung cancer in Japan.

Group	Year established	Chairman	Number of facilities	Allowance for personal membership	Number of members	Data center	Financial resource	Phase III studies	References
JCOG	1990	Yuichiro Ohe	38	+	4600	+	A	+	[3,4]
WJOG	1992	Yoichi Nakanishi	187	+	1000	+	A, C, D, E	+	[1,5,6]
OLCSG	1995	Katsuyuki Kiura	20	+	110	–	D	+	[7]
TCOG	2001	Minoru Kurihara	37	+	77	–	C, D, E	+	[8,9]
CJLSG	2003	Hiroshi Saito	30	+	100	–	A, B, C, D	–	[10–12]
TORG	2004	Koshiro Watanabe	52	+	90	+	C, D	–	[13–16]
LOGIK	2004	Hiroshi Semba	89	+	322	–	F	–	[17,18]
NEJSG	2006	Toshihiro Nukiwa	108	+	20	–	A, C, D	+	[19–21]

A: National grant, B: Other grant, C: Donation, D: Membership fee, E: Consigned research fund, F: Clinical Research Support Center Kyushu.
Japan Clinical Oncology Group, JCOG; West Japan Oncology Group, WJOG; Okayama Lung Cancer Study Group, OLCSG; Tokyo Cooperative Oncology Group, TCOG; Central Japan Lung Study Group, CJLSG; Thoracic Oncology Research Group, TORG; Lung Oncology Group in Kyushu, LOGIK; North East Japan Study Group, NEJSG.

cancer groups in the late 2000s. Hiroshi Ariyoshi, the original chair of WJTOG, was succeeded in 2004 by Masahiro Fukuoka, who in turn was succeeded in 2009 by Yoichi Nakanishi. The missions of WJOG are to carry out clinical trials and to educate oncologists and patients with regard to appropriate cancer treatments and clinical studies. The data center was initially set up in 1998 at Kinki University Faculty of Medicine under the direction of Kazuhiko Nakagawa, and it subsequently relocated to Namba, Osaka, in 2004 (Fig. 1). At present, the WJOG Data Center is staffed by eight data managers led by Shinichiro Nakamura and ensures the adequacy, integrity, and quality of the data for patients enrolled in clinical trials. A total of 187 institutions across the country participate in clinical lung cancer research performed by WJOG.

WJTOG performed a multicenter, randomized, open-label, phase III trial (WJTOG3405) of first-line treatment with gefitinib versus cisplatin plus docetaxel in patients with advanced non-small-cell lung cancer (NSCLC) positive for activating mutations of the epidermal growth factor receptor (*EGFR*) gene [5]. The study demonstrated the superiority of gefitinib over cisplatin plus docetaxel in terms of its primary end point of progression-free survival (PFS). This was the first published report establishing the proof of concept that molecularly targeted agents are far more effective than conventional chemotherapy when administered to the appropriate genetically defined patient population. WJOG is currently conducting a phase III trial for patients with completely resected *EGFR* mutation-positive NSCLC of p-stage II or III. In this trial (WJOG6410L), patients are randomized to receive gefitinib (250 mg/day, 2 years) or cisplatin plus vinorelbine (four cycles), and the primary end point is disease-free survival.

WJOG also has two ongoing phase III trials of continuation maintenance therapy for advanced NSCLC. In WJOG5610L, patients with advanced nonsquamous NSCLC negative for *EGFR* mutations are initially treated with the combination of pemetrexed, carboplatin, and bevacizumab (Fig. 2B). Those individuals who complete four cycles of this treatment without disease progression are then randomized to receive bevacizumab alone or bevacizumab plus pemetrexed, with the goal of identifying an optimal maintenance regimen that improves OS. WJOG recently completed a multicenter randomized phase III study comparing carboplatin plus S-1 with carboplatin plus paclitaxel as a first-line treatment in patients with advanced NSCLC [1]. The primary objective of this Lung Cancer Evaluation of TS-1 (LETS) study—determination of the non-inferiority of carboplatin and S-1 compared with carboplatin and paclitaxel in terms of OS—was met. On the basis of the trial results, the Japanese guidelines for lung cancer treatment were updated to include carboplatin plus S-1 as one of the standard platinum-based regimens for first-line treatment of advanced NSCLC. Subsequent survival analysis according to histological subtype of NSCLC revealed that carboplatin plus S-1 showed a tendency to improve OS, with a 3.4-month increase in median OS compared with carboplatin plus paclitaxel (14.0 months versus 10.6 months; hazard ratio of 0.713 and 95% confidence interval of 0.476–1.068), for patients with squamous NSCLC [6]. This outcome is of particular interest because of the limited therapeutic options available for this patient population compared with patients with nonsquamous cell carcinoma. On the basis of

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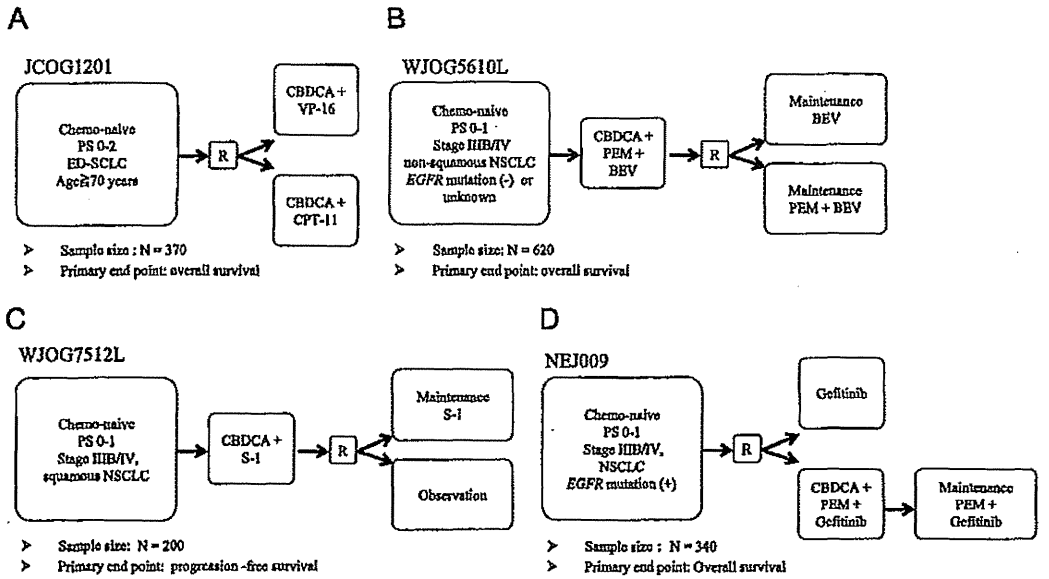

Fig. 2 – Ongoing phase III trials for advanced lung cancer in Japan. (A) JCOG1201. (B) WJOG5610L. (C) WJOG7512L. (D) NEJ009. Abbreviations: PS, performance status; R, randomization; CBDCA, carboplatin; VP-16, etoposide; CPT-11, irinotecan; PEM, pemetrexed; BEV, bevacizumab.

these results, WJOG is now conducting a randomized phase III trial for squamous NSCLC (WJOG7512L) (Fig. 2C), in which patients treated with four cycles of carboplatin plus S-1 are randomized to receive single-agent S-1 maintenance therapy or observation. Depending on the outcome, this would be the first study to establish the benefit of maintenance therapy for patients with squamous NSCLC.

Collaboration with JCOG is also an important activity of WJOG. JCOG1210/WJOG7813L, a randomized phase III trial comparing single-agent docetaxel with pemetrexed plus carboplatin followed by pemetrexed maintenance for elderly (≥75 years) individuals with nonsquamous NSCLC, is ongoing (Fig. 3A).

2.3. *Okayama Lung Cancer Study Group*

The Okayama Lung Cancer Study Group (OLCSG) was founded in 1995 to conduct multi-institutional clinical trials and now consists of 20 institutions in the Chugoku and Shikoku districts affiliated with the former Second Department of Internal Medicine at Okayama University Medical School (Table 1). During the last two decades, the group has published more than 20 research studies, some of which have been included in meta-analyses of prophylactic cranial irradiation in patients with SCLC and of thoracic irradiation and chemotherapy in those with limited disease SCLC. More recently, OLCSG performed a phase III trial of cisplatin, docetaxel, and concurrent thoracic irradiation in patients with locally advanced NSCLC (OLCSG 0007), the results of which informed the Japanese guidelines for the treatment of NSCLC [7]. The data for OLCSG 0007 were managed at Okayama University and Aichi Cancer Center Research Institute, whereas the statistical analysis was performed at the latter institution. OLCSG has not outsourced data management to an independent external data center, but it is now planning to do so for better quality assurance.

Over the last decade, substantial progress has been made in the development of genotype-based targeted therapies for advanced NSCLC. The discovery of somatic mutations in the tyrosine kinase domain of the EGFR and of the association of such mutations with a high response rate to EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib has had a profound impact on the treatment of metastatic NSCLC. This molecular basis for therapy selection may also be applicable to patients with locally advanced NSCLC, for whom targeted therapies remained to be established. OLCSG and LOGIK (see Section 2.7) are now conducting an intergroup trial to evaluate induction therapy with single-agent gefitinib followed by cisplatin, docetaxel, and concurrent thoracic irradiation for patients with EGFR mutation-positive locally advanced NSCLC (Fig. 3B).

2.4. *Tokyo Cooperative Oncology Group (TCOG)*

The Tokyo Cooperative Oncology Group (TCOG) was established in 1972 for the purpose of performing multi-institutional cooperative clinical trials of treatments for inoperable cancers of various organs, with Kiyoji Kimura (a former vice director of National Cancer Center Hospital) as its first organizer (Table 1). Its early research results with N1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207) in 1974 and with 5-fluorouracil (5-FU) in 1975 led to the approval of these agents for clinical use in Japan. On the basis of its active clinical studies and continuing educational activities including monthly medical conferences and annual summer seminars, the group was certified as a nonprofit organization (NPO) by the Tokyo Metropolitan Government in 2001. The first leaders included Hisanobu Niitani as president and five other directors.

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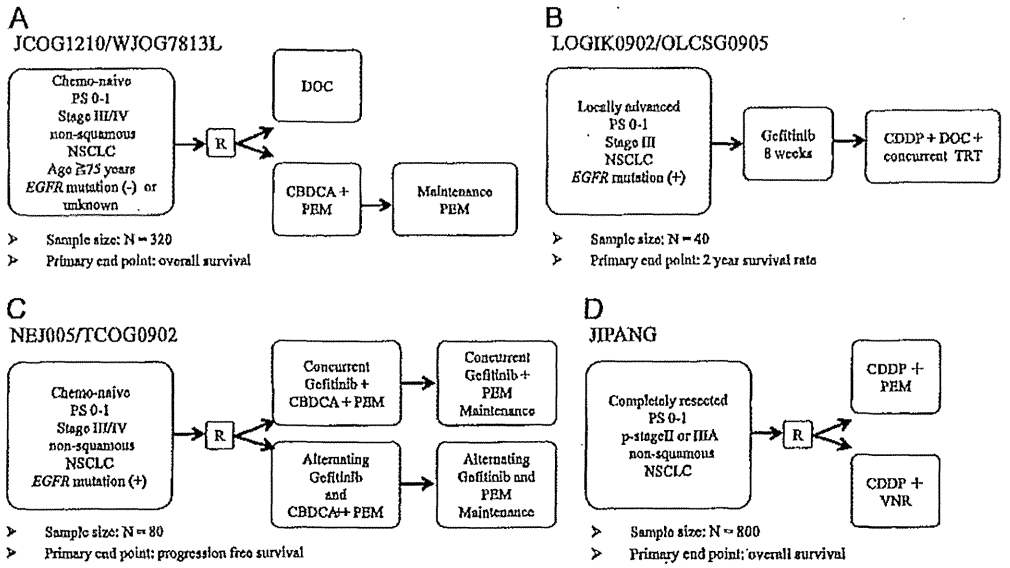

Fig. 3 – Recent intergroup trials for lung cancer in Japan. (A) JCOG1210/WJOG7813L. (B) LOGIK0902/OLCSG0905. (C) NEJ005/TCOG0902. (D) JIPANG. Abbreviations: PS, performance status; R, randomization; DOC, docetaxel; CBDCA, carboplatin; PEM, pemetrexed; TRT, thoracic radiotherapy; p-stage, pathological stage; CDDP, cisplatin; VNR, vinorelbine.

TCOG now consists of 37 institutions and is currently conducting clinical trials mostly in thoracic and gastrointestinal oncology. It has a clinical trial registration center and six committees for academic planning, clinical trial planning, clinical trial evaluation, overall trial monitoring, data and safety monitoring, and statistical analysis. For phase I and II studies, data management is carried out by the clinical trial registration center, and statistical considerations and analysis are the responsibility of the principal investigators with voluntary consultation of the statistical analysis committee. Because of a shortage of human resources, however, data management and statistical analysis for phase III studies are largely outsourced. TCOG has held monthly conferences for the past 33 years with ~70 participants at each meeting and annual summer seminars for the past 14 years with ~500 multidisciplinary team professionals in attendance. It has published >30 research articles on clinical trials in Japanese or English, which were accompanied by presentations at various medical conferences including those of the Japan Society of Clinical Oncology, American Society of Clinical Oncology, and European Society for Medical Oncology [8,9]. Since 2006, TCOG has also cooperated with the North East Japan Study Group (NEJSG, see Section 2.8) on lung cancer trials, with more than seven trials to date (Fig. 3C).

2.5. *Central Japan Lung Study Group*

The Central Japan Lung Study Group (CJLSG) was established in 2003 as an NPO to promote the prevention and diagnosis of, the performance of clinical trials for, and education about respiratory diseases (Table 1). The first chairperson of the group was Kaoru Shimokata. CJLSG consists of 30 facilities located mainly in central Japan, and most of its members are medical doctors who work in regional or university hospitals. CJLSG is supported by member fees and donations, and it holds educational seminars on several aspects of respiratory medicine including clinical trials, bronchoscopy, and clinical statistics for young doctors.

CJLSG has published the results of several clinical trials in international scientific journals [10–12] and is currently conducting 14 trials related to pneumonia, molecular biology, supportive care, and chemotherapy in lung cancer patients. CJLSG is now planning PREDICT1, a prospective observational survey of predictors of responses based on the analysis of blood samples for chemotherapy with carboplatin plus pemetrexed in patients with nonsquamous NSCLC.

2.6. *Thoracic Oncology Research Group*

The Thoracic Oncology Research Group (TORG) was founded as an NPO in 2004 (Table 1). It currently consists of 52 collaborative institutions, and it is chaired by Koshiro Watanabe; the TORG has published four studies to date [13–16]. The TORG data center promotes quality control of clinical trials by contributing to patient registration, data collection and management, and central monitoring. The monitoring reports are submitted to and reviewed by an independent monitoring committee and study investigators on a semiannual basis. Interim analysis is performed when a preplanned number of patients have been enrolled during the study period. In addition, TORG has taken appropriate advice from several biostatisticians when conducting new clinical trials or analyzing trial data.

TORG has seven and 11 trials in accrual and follow-up phases, respectively. Although TORG has no experience in conducting large-scale randomized trials, three studies have registered 100 or more patients. The policies of TORG are to initiate

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well-designed and timely clinical trials as soon as feasible and to finish the trials adequately and as rapidly as possible.

2.7. *Lung Oncology Group in Kyushu*

The Lung Oncology Group in Kyushu (LOGiK) was established in 2004 as a voluntary cooperative group to perform multicenter clinical trials for thoracic malignant diseases, mainly lung cancer, and is headquartered at the Research Institute for Diseases of the Chest at Kyushu University (Fig. 1, Table 1). It comprises a large network of medical oncologists, thoracic surgeons and physicians, radiologists, pathologists, and biostatisticians at public and private institutions across the country, although most LOGiK member institutions are located in Kyushu districts. As of 10 January 2014, the group had 322 members affiliated with 89 medical institutions. The operational policy of the group is decided at regularly held board meetings. Plans for clinical trials can be proposed by any member of the group and are discussed in detail by the protocol committee and, as necessary, by the pathology committee or radiology committee. The activities of the group are funded and supported by the Clinical Research Support Center Kyushu (CReS Kyushu), whose services include various aspects of clinical trials such as registration and assignment of patients, trial monitoring, collection of case report forms, and data cleaning. The biostatistics committee at CReS Kyushu meets regularly with contact biostatisticians to analyze clinical trial data or provide advice for trial planning. LOGiK has conducted various phase II and feasibility trials for lung cancer [17,18] and currently has 13 active clinical trials.

2.8. *North East Japan Study Group*

In January 2006, 35 institutions belonging to four Japanese regional groups in Hokkaido, Tohoku, Saitama, and Tokyo joined together to conduct a phase II study (NEJ001) and a phase III study (NEJ002) of patients with EGFR mutation-positive NSCLC screened with the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method developed by Koichi Hagiwara (Table 1). This North East Japan Study Group (NEJSG) was established with the assistance of Hisanobu Niitani, who was the chairperson of TCOG. Together, NEJ001 and NEJ002 showed that EGFR-TKI treatment conferred long-term PFS and a better quality of life and thereby helped to open the door to personalized medicine in the field of lung cancer [19–21]. NEJSG became an NPO in December 2010 for the performance of clinical studies in which biological investigation is important. The aim of NEJSG is to develop, conduct, coordinate, and stimulate translational and clinical research to improve the management of lung cancer and related problems and to increase the survival and quality of life of affected individuals. At present, 108 institutions located in the original four regions as well as in two additional regions (Tochigi and Niigata) are active in NEJSG studies.

NEJSG is currently conducting a randomized phase III study comparing single-agent gefitinib with the combination of carboplatin-pemetrexed and gefitinib followed by continuation maintenance therapy with pemetrexed and gefitinib in patients with advanced nonsquamous NSCLC positive for activating mutations of EGFR (Fig. 2D). The primary end point of this study is the OS.

3. Conclusions and future perspectives

Although only eight cooperative study groups in Japan are reviewed here because of space limitations, several other Japanese groups are also conducting clinical trials for lung cancer. The establishment of multiple study groups to perform clinical trials for this single disease is indicative of the high priority given to the development of new treatment strategies for lung cancer through such trials in Japan, but it also presents several challenges. First, it may be difficult for all such groups to be associated with a data center that maintains data quality, ensures the scientific integrity of trial results, and minimizes the risk to enrolled patients. Second, the number of clinical trials that target small subsets of patients with specific driver oncogenes, specific histological subtypes of lung cancer, poor performance status, or advanced age is increasing. Overlap in such trials performed by different groups and institutional overlap among clinical trial groups do not represent optimal use of limited resources. Third, the number of groups that are able to complete phase III trials is limited to date, given the large sample size required and the complexity of data management for such trials. The division of roles in each cooperative study groups is essential to improve efficiency of clinical trials in Japan.

To overcome these challenges, Japanese cooperative groups have increased the extent of their collaboration. Indeed, several intergroup clinical trials for advanced NSCLC (including those performed by JCOG and WJOG, NEJSG and TCOG, and OLCSG and LOGiK) are now ongoing (Fig. 3A–C). In addition, seven Japanese cooperative groups are working together to conduct a large randomized phase III trial comparing cisplatin plus vinorelbine with cisplatin plus pemetrexed in patients with completely resected nonsquamous NSCLC of p-stage II or III (Fig. 3D). The primary end point of this study is the OS, and a total of 800 patients will be enrolled. The study, named JIPANG, was designed to test a new application of pemetrexed to adjuvant chemotherapy in Japan. Smooth implementation of such intergroup studies requires abundant funds; however, Japan does not seem to have an effective national funding system for cooperative study groups. In United State of America, the National Cancer Institute has provided enormous funds for the consolidation of several cooperative groups and the merging of groups focused on a single disease site or modality with multidisciplinary groups.

Although institutional barriers to the performance of such large intergroup trials remain, further harmonization and collaboration among cooperative groups will be important in allowing Japanese investigators to generate new data that can change clinical practice and improve the clinical outcome of lung cancer patients.

Conflict of interest

Isamu Okamoto received honoraria from Pfizer Co., Eli Lilly K.K., and Taiho Pharmaceutical Co. Ltd.; Yuichiro Ohe

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received honoraria from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., and Daiichi Sankyo Co., Ltd. and research funding from Chugai Pharmaceutical Co. Ltd., Pfizer Co., AstraZeneca K.K., and Merck Serono, Eisai; Kazuhiko Nakagawa received honoraria from Abbott Japan Co. Ltd., Eli Lilly K.K., Takeda Bio Development Center Ltd., Daiichi Sankyo Co. Ltd., AstraZeneca K.K., Kyowa Hakko Kirin Co. Ltd., and Chugai Pharmaceutical Co. Ltd., and research funding from Chugai Pharmaceutical Co. Ltd., AstraZeneca K.K., Nippon Boehringer Ingelheim Co. Ltd., and Daiichi Sankyo Co. Ltd. and subsidies from Daiichi Sankyo Co. Ltd., Taiho Pharmaceutical Co. Ltd., and Ono Pharmaceutical Co. Ltd.; Katsuyuki Kiura received honoraria from Pfizer Co., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd, and Eli Lilly K.K., and research funding from Phizer Co., Chugai Pharmaceutical Co. Ltd., Novartis Pharmaceutical K.K., and Daiichi Sankyo Co. Ltd. and subsidies from Sanofi K.K. and Chugai Pharmaceutical Co. Ltd.; Yuichi Takiguchi received honoraria from AstraZeneca K.K, Chugai Pharmaceutical Co. Ltd., Sanofi K.K., and Titan Ltd.; Koichi Takayama received honoraria from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., Phizer Co., and AstraZeneca K.K. and research grants from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., Kyowa Hakko Kirin Co. Ltd., and Phizer Co.; Masahiro Tsuboi received honoraria from AstraZeneca K.K., Eli Lilly K.K., Johnson and Johnson, Chugai Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co. Ltd.; Nobuyuki Yamanoto received honoraria from Taiho Pharmaceutical Co. Ltd., Pfizer Co., Chugai Pharmaceutical Co. Ltd., AstraZeneca K.K., and Ono Pharmaceutical Co. Ltd.; Toshihiro Nukiwa received honoraria from Shionogi Pharmaceuticals and Boehringer Ingelheim Co. Ltd., research funding from AstraZeneca K.K. and Chugai Pharmaceutical Co. Ltd., and other fees from Sekisui Diagnostics; Hideo Saka received research funding from Daiichi Sankyo Co. Ltd., Ono pharmaceutical Co., AstraZeneca K.K., Novartis Pharmaceutical K.K., Eisai Co., Kyowa Hakko Kirin Co. Ltd., and Eli Lilly K.K.; Hiroaki Okamoto received research funding from Eli Lilly K.K., Chugai Pharmaceutical Co. Ltd., and Dainippon Sumitomo Pharma; the other authors have no conflict of interest.

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Adjuvant Chemotherapy in Patients with Completely Resected Small Cell Lung Cancer: A Retrospective Analysis of 26 Consecutive Cases

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Objective: Several clinical studies have demonstrated the efficacy and safety of adjuvant chemotherapy in patients with completely resected small cell lung cancer for a selected limited stage. However, it is unclear whether adjuvant chemotherapy is feasible in clinical practice. The objective of this study was to analyze the efficacy and safety of adjuvant chemotherapy for small cell lung cancer patients retrospectively in clinical practice.
Methods: From January 2002 to March 2012, 56 small cell lung cancer patients underwent surgery as initial therapy in our institute. Of these, 26 patients received adjuvant chemotherapy. The clinical data of patients who received adjuvant chemotherapy were retrospectively analyzed.
Results: The chemotherapy regimens were cisplatin and irinotecan in 16 patients, cisplatin and etoposide in 1 and carboplatin and etoposide in 9. Median follow-up time was 44.8 months. Nineteen (73%) patients received the full course of chemotherapy. Median recurrence-free survival was 21.4 months. Median survival time was not reached. There was no treatment-related death.
Conclusion: Adjuvant chemotherapy may be generally safe and efficacious in selected small cell lung cancer patients.

Key words: small cell lung cancer – surgery – adjuvant chemotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancers. It is a virulent, rapidly growing, early metastasizing and invasive cancer. At diagnosis, approximately 90% of patients with SCLC already have regional or distant spread (1). Furthermore, it is difficult to diagnose SCLC presenting as a solitary small nodule of the lung by transbronchial lung biopsy. As a result, SCLC presenting as a solitary small nodule is often diagnosed at the time of therapeutic surgical resection. In these cases, we commonly administer additional chemotherapy after surgery in clinical practice to control micro metastases. A previous clinical study, case series and a meta-analysis showed that adjuvant chemotherapy might be feasible and reduce the risk of recurrence in SCLC patients (2–4). In addition, Tsuchiya et al. (5) reported that surgical resection followed by cisplatin and etoposide chemotherapy was feasible. The European Society for Medical Oncology (ESMO) and American College of Chest Physicians (ACCP) guidelines recommend adjuvant chemotherapy for SCLC patients. However, it was unclear that adjuvant

chemotherapy for SCLC patients was efficacy and safety in clinical practice. Therefore, the efficacy and safety of adjuvant chemotherapy for SCLC patients were retrospectively analyzed.

PATIENTS AND METHODS

The current study included 56 consecutive patients with histologically proven SCLC who underwent complete resection at the National Cancer Center Hospital (NCCH) from January 2002 to March 2012. The medical records of SCLC patients who received adjuvant chemotherapy were retrospectively reviewed. Patients who had post-operative recurrence before starting adjuvant chemotherapy, patients who had difficulty with adjuvant chemotherapy due to complications, and patients who refused were excluded. No patients had received any treatment such as chemotherapy or irradiation before surgery. Histological diagnoses and tumor grades were determined in accordance with TNM staging (seventh edition) (6). The following data were extracted: (i) patients' characteristics: age, sex and Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the start of adjuvant chemotherapy, clinical stage before surgery, pathological stage after surgery and histological diagnosis before and after surgery; (ii) type of chemotherapeutic agents administered, dose, treatment cycle, relative dose intensity and toxicity; and (iii) patterns of recurrence, recurrence-free survival time (RFS) and overall survival time (OS) data. All the patients gave their written informed consent to analyze their medical records after treatments. This study was approved by the Institutional Review Board of NCCH.

Treatment Schedule

The chemotherapy regimens were cisplatin and irinotecan (IP), cisplatin and etoposide (EP) and carboplatin and etoposide (CE). The doses of the chemotherapeutic agents were: cisplatin (60 mg/m^2 on Day 1) and irinotecan (60 mg/m^2 on Days 1, 8 and 15) repeated every 4 weeks; cisplatin (80 mg/m^2 on Day 1) and etoposide (100 mg/m^2 on Days 1–3) repeated every 3 weeks; and carboplatin (AUC = 5 on Day 1) and etoposide (80 mg/m^2 on Days 1–3) repeated every 3 weeks. All regimens consisted of a total of four cycles. The efficacy and safety of each regimen has been established in previous clinical trials (5,7,8).

Assessment and Analysis

Safety and tolerability were assessed during the adjuvant chemotherapy. Adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. RFS and OS were measured from the date of surgery until recurrence and death or the final day of the follow-up period, and median survival was calculated using the Kaplan–Meier method. STATA version 12 (StataCorp LP, College Station, TX, USA) was used for all analyses.

Table 1. Patients' characteristics

Characteristic	*N*
Twenty-six patients received adjuvant chemotherapy	
Total	26
Sex	
Male/female	19/7
Age	
Median (range)	67 (46–84)
ECOG PS	
0/1	21/5
Clinical stage	
I (T1N0M0/T2aN0M0)	22 (17/5)
II (T1N1M0/T2aN1M0/T3N0M0)	4 (1/2/1)
III 0	
Pathological stage	
I (T1N0M0/T2aN0M0)	10 (6/4)
II (T2bN0M0/T1N1M0/T2N1M0/T3N0M0)	9 (1/2/4/2)
III (T1N2M0/T2N2M0/T3N2M0)	7 (4/2/1)
Pathological histology	
Small cell carcinoma	18
Combined small cell carcinoma	
With adenocarcinoma	4
With large cell carcinoma	4
Thirty patients received surgery alone	
Total	30
Sex	
Male/female	25/5
Age	
Median (range)	71 (57–89)
ECOG PS	
0/1	13/17
Clinical stage	
I (T1N0M0/T2aN0M0)	25 (21/4)
II (T1N1M0/T2N1M0)	4 (2/2)
III (T3N1M0)	1 (1)
Pathological stage	
I (T1N0M0/T2aN0M0)	18 (15/3)
II (T1N1M0/T2N1M0/T3N0M0)	7 (3/2/2)
III (T1N2M0/T2N2M0/T3N2M0/T4N2M0/T3N3M0)	5 (1/1/1/1 /1)
Pathological histology	
Small cell carcinoma	19
Combined small cell carcinoma	
With adenocarcinoma	4
With large cell carcinoma	4
With squamous cell carcinoma	3

ECOG PS, Eastern Cooperative Oncology Group Performance Status; *N*, number of patients.

RESULTS

Patient Characteristics

A total of 56 consecutive patients with SCLC were sampled from the hospital-based registry of the NCCH between January 2002 and March 2012. The characteristics of the patients are listed in Table 1. All patients underwent surgery as initial treatment. The surgical procedures were pulmonary lobectomy in 55 patients and partial resection in one patient. Thirty patients were excluded for reasons such as death not relevant to surgery ($n = 1$), early post-operative recurrence ($n = 2$), thoracic empyema after surgery to need antibiotics for long periods ($n = 2$), severe complications ($n = 4$) and poor general condition including old age ($n = 5$) (Fig. 1). As a result, 26 patients who received adjuvant chemotherapy were reviewed in this study.

Discrepancy Between Clinical and Pathological Histology Findings and Stages

Only 9 patients had a confirmed diagnosis of SCLC and 13 patients did not have a confirmed diagnosis before surgery. On the other hand, in four patients, the confirmed diagnosis was changed to SCLC. Their pre-operative diagnoses included one adenocarcinoma, one squamous cell carcinoma, one large cell carcinoma and one carcinoma not otherwise specified, respectively. As a consequence of surgery, combined SCLC types with adenocarcinoma or squamous cell carcinoma were found in 8 (30.8%) patients. Twenty-two patients had pre-operative clinical Stage I disease and four had Stage II disease. However, post-operative pathological Stage I, II and III disease was found in 10, 9 and 7 patients, respectively (Table 1).

Chemotherapy Regimens

The chemotherapy regimen was selected by each physician. Sixteen patients received IP, one received EP and nine received CE (Table 2). The median age of the patients who received IP was 65 years (range, 47–72 years), while that of patients who received CE was 75 years (range, 62–84 years). Most patients who were 70 years of age or older received CE (88.9%).

Treatment Delivery and Relative Dose Intensity

The median duration from surgery to starting chemotherapy was 51 days (range, 26–78 days). Table 3 shows treatment delivery for each regimen. Nineteen (73%) patients received four cycles of chemotherapy. Seven (27%) patients did not

Table 2. Regimen selected

	Number of patients	Median age (range)	ECOG PS 0/1 (*N*)
IP	16	65 (47–72)	10/6
EP	1	46	1/0
CE	9	75 (62–84)	4/5

IP, cisplatin and irinotecan; EP, cisplatin and etoposide; CE, carboplatin and etoposide.

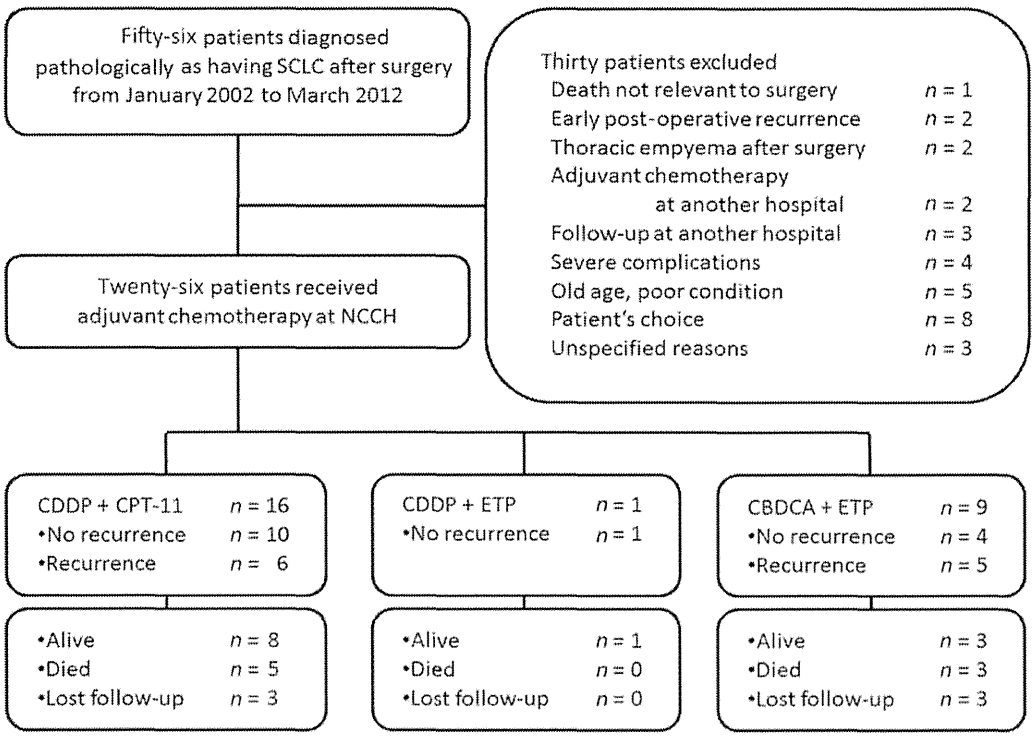

Figure 1. Follow-up of the study patients by treatment group after surgery.

complete the initially planned chemotherapy because of adverse events (AE). The relative dose intensity was 83.6% in IP, 87.5% in EP, and 86.8% in CE.

Safety Analysis

Chemotherapy-related toxicity is shown in Table 4. Grade 4 AEs were found in 14 (53.8%) patients: neutropenia in 11 patients, thrombocytopenia in 2 patients and febrile neutropenia in 1 patient. Adjuvant chemotherapy for completely resected SCLC patients was feasible. All AEs were manageable, and there was no treatment-related death. We had to stop or change chemotherapy regimens due to AEs in four patients received IP and three patients received CE. In IP, two patients were changed to EP due to hepatic toxicity, one patient was changed to CE due to kidney failure and one patient could not continue to receive chemotherapy due to brain bleeding. In CE, all three patients discontinued chemotherapy due to fatigue and allergy. These three patients were over the age of 70 years (Table 3).

Efficacy Analysis

Of the 26 patients, 18 (69.2%) were still alive after the median follow-up of 44.8 months (range, 2.8–78.1 months). The median RFS of all patients was 21.4 months (95% CI: 14.6–41.3 months); the median RFS was 17.8 months (95% CI: 12.8–46.5 months) with IP and 23.0 months with CE (95% CI: 10.2–61.9 months) (Fig. 2A). The median survival time of all patients could not be calculated due to the insufficient follow-up time. The estimated 3-year and 5-year survivals were 68.9% (95% CI: 42.3–84.6%) and 51.7% (95% CI: 24.0–73.2%), respectively (Fig. 2B). On the other hand, the estimated 3-year and 5-year survivals of 30 patients received surgery alone were 60.5% (95% CI: 39.9–76.0%) and 45.4% (95% CI: 25.0–63.8%), respectively.

Table 3. Treatment delivery

Number of treatment cycles	IP ($N = 16$)	EP ($N = 1$)	CE ($N = 9$)	Total ($N = 26$)
4	12 (75%)	1 (100%)	6 (67%)	19 (73%)
3	–	–	1 (11%)	1 (4%)
2	–	–	1 (11%)	1 (4%)
1	4 (25%)	–	1 (11%)	5 (19%)

Table 4. Chemotherapy-related toxicity by CTC-AE ver. 4.0

	Grade				
Toxicity	1	2	3	4	3/4
Anemia	10	3	2	0	2 (8)
Neutropenia	1	0	3	11	14 (54)
Febrile neutropenia	0	0	2	1	3 (12)
Thrombocytopenia	1	3	3	2	5 (19)
Nausea	12	3	1	0	1 (4)
Appetite loss	11	5	0	0	0 (0)
Diarrhea	7	5	1	0	1 (4)
Fatigue	8	2	1	0	1 (4)
Hepatic dysfunction	1	0	2	0	2 (8)
Renal failure	1	1	0	0	0 (0)

Values are N (%).

Patterns of Recurrence

Recurrence was confirmed in 10 (38.5%) patients, and the initial recurrence site was mediastinal lymph nodes in three patients, lung in three, bone in three and abdominal lymph node in one. Recurrence was found in two patients with pathological Stage I, four patients with Stage II, and four patients with Stage IIIA.

DISCUSSION

Although the standard treatment for most cases of limited SCLC is considered to be chemoradiotherapy, clinical T1 and T2 SCLC without evidence of lymph node involvement (N0) can be considered for surgical resection. Previous reports suggested that these selected patients might benefit from surgery expecting radical cure (9–11). In addition, combination surgery and adjuvant chemotherapy or post-operative irradiation has a 5-year survival of approximately 40–70% (2–5). However, it is difficult to diagnose T1 and T2 SCLC presenting as a solitary pulmonary nodule prior to surgery despite development of less invasive diagnostic methods such as transbronchial lung biopsy, endobronchial ultrasonography and CT-guided lung biopsy (12). As a result, SCLC presenting as a solitary pulmonary nodule is often diagnosed at the time of therapeutic resection. In the present analysis, 13 patients underwent surgery with uncertain pathological diagnoses. Furthermore, four patients had a diagnosis of NSCLC before surgery. According to previous reports, approximately 5–10% of patients diagnosed with SCLC will have other pathologies such as adenocarcinoma or squamous cell carcinoma within the surgically resected specimens (13,14). As a consequence of surgery, combined SCLC types with adenocarcinoma or squamous cell carcinoma were found in 8 (30.8%) patients. We have no defined treatment strategy for combined SCLC (containing any other NSCLC component). However, it has been reported that there is no difference in the prognosis between SCLC and combined SCLC (15). In our perspective, surgery would be the best treatment choice for early stage combined SCLC.

There have been no Phase III trials of adjuvant chemotherapy for SCLC. A previous clinical study, a case series, and a meta-analysis showed that adjuvant chemotherapy including cisplatin may be feasible and reduce the risk of recurrence in SCLC patients (2–4). The feasibility of EP after surgical resection has

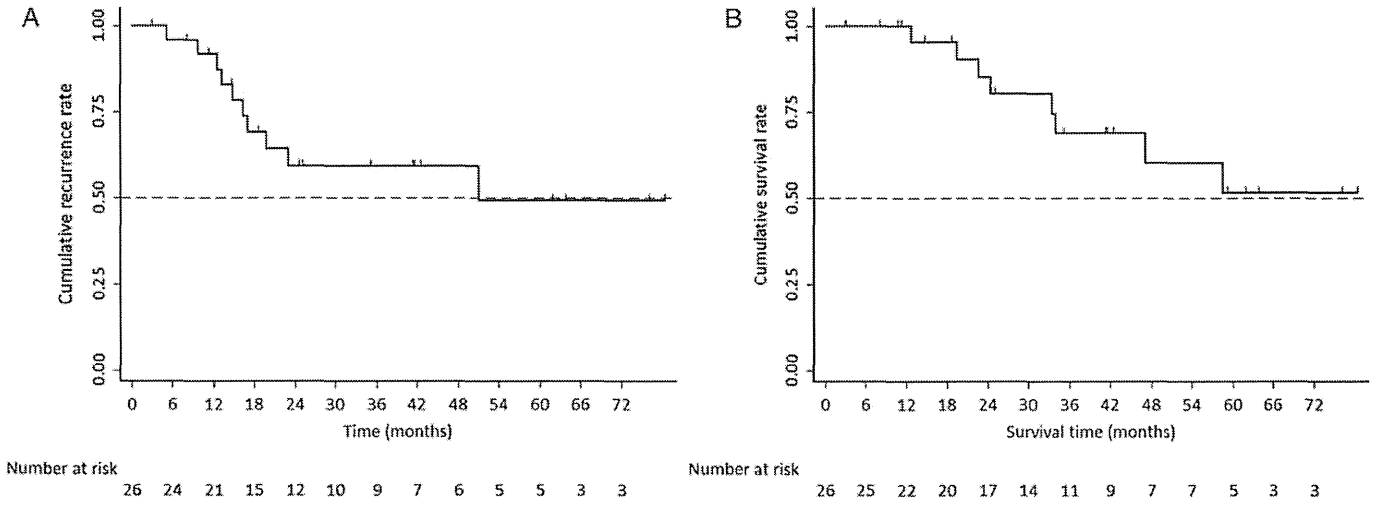

Figure 2. (A) Recurrence-free survival among the study patients. Kaplan–Meier curves for recurrence-free survival are shown for the recurrence-free survival population. (B) Overall survival among the study patients. Kaplan–Meier curves for overall survival are shown for the overall survival population.

been reported from Japan (2,5). Therefore, it remains unclear which regimen is appropriate. According to previous clinical trials of extensive disease-SCLC (7,8), EP, IP and CE were selected for adjuvant chemotherapy regimens. In the present analysis, the choice of regimen was left to the physician by reference to previous clinical trials (5,7,8). Regarding efficacy, we consider that IP and CE were not apparently inferior to EP in a previous Phase II study (JCOG 9101) in which the estimated 3-year and 5-year survivals were 61 and 57%, respectively.

The CE regimen has been used in elderly or poor-risk patients with extensive disease-SCLC (8). In the present analysis, CE had acceptable toxicities and reproducible efficacy in this population. In the period of the present analysis, surgery was performed as initial therapy for 56 SCLC patients at the NCCH. Of these, 30 patients could not receive adjuvant chemotherapy for any reason. Therefore, those who received surgery and adjuvant chemotherapy in this study were highly selected. Thirty patients received surgery alone tended to be in higher median age and in poor PS compared with these received adjuvant chemotherapy. But, we could not show clearly-defined cut-off line of adjuvant chemotherapy. It is the limitation of this retrospective study.

A phase III trial of EP versus IP for adjuvant chemotherapy (UMIN 000010298) is now ongoing in patients diagnosed with high-grade pulmonary neuroendocrine carcinoma (large cell neuroendocrine carcinoma and small cell lung cancer) by the Japan Clinical Oncology Group (JCOG).

Adjuvant chemotherapy of selected SCLC patients may be generally safe and efficacious. Further studies should be considered to evaluate the therapeutic possibility of adjuvant chemotherapy in SCLC patients.

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Conflict of interest statement

None declared.

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Cyclooxygenase-2 inhibitors for non-small-cell lung cancer: A phase II trial and literature review

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Abstract. Several preclinical and clinical studies have demonstrated that cyclooxygenase-2 (COX-2) inhibitors are efficient for the treatment of non-small-cell lung cancer (NSCLC). However, two recent phase III clinical trials using COX-2 inhibitors in combination with platinum-based chemotherapy failed to demonstrate a survival benefit. Thus, validation and discussion regarding the usefulness of COX-2 inhibitors for patients with NSCLC are required. We conducted a prospective trial using COX-2 inhibitors for the treatment of 50 NSCLC patients accrued between April, 2005 and July, 2006. Patients with untreated advanced NSCLC received oral meloxicam (150 mg daily), carboplatin (area under the curve = 5 mg/ml x min on day 1) and docetaxel (60 mg/m^2 on day 1) every 3 weeks. The primary endpoint was response rate. The response and disease control rates were 36.0 and 76.0%, respectively. The time-to-progression (TTP) and overall survival (OS) were 5.7 months [95% confidence interval (CI): 4.6-6.7] and 13.7 months (95% CI: 11.4-15.9), respectively. The 1-year survival ratio was 56.0%. Grade 3 neuropathy was observed in only 1 patient. We performed tumor immunohistochemistry for COX-2 and p27 and investigated the correlation between their expression and clinical outcome. COX-2 expression in the tumor tended to correlate with a higher response rate (50.0% in the high- and 18.2% in the low-COX-2 group; P=0.092). Based on our results and previous reports, various trial designs, such as the prospective use of COX-2 inhibitors only for patients with COX-2-positive NSCLC, including the exploratory analysis of biomarkers associated with the COX-2 pathway, may be worth further consideration.

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Key words: non-small-cell lung cancer, cyclooxygenase-2, p27, carboplatin, docetaxel

Introduction

Cyclooxygenase-2 (COX-2), the enzyme that converts arachidonic acid to prostaglandins (PGs), is expressed in a number of solid tumors and is associated with carcinogenesis, tumor proliferation, infiltration, metastasis, angiogenesis and resistance to anticancer drugs (1). In lung cancer cells, COX-2, which is particularly overexpressed in adenocarcinoma (2), is considered to be a negative predictor of survival in this subpopulation (3-7). Based on these reports, several clinical trials have been conducted for the potentiation of targeting COX-2 in lung cancer (8).

The cyclin-dependent kinase (Cdk) inhibitor p27 plays a critical role in cell cycle regulation from the G1 to the S phase by inhibiting Cdk4/6-cyclin D1 and Cdk2-cyclin E (9). Loss of p27 expression tends to be an unfavorable prognostic factor in patients with non-small-cell lung cancer (NSCLC) (10). Increased p27 expression is attributed to COX-2-independent mechanisms of G0/G1 arrest driven by COX-2 inhibitors (11). Thus, p27 expression may be another predictive factor of the response to COX-2 inhibitors.

Taxanes, such as paclitaxel and docetaxel, are microtubule-stabilizing agents that act by interfering with spindle microtubule dynamics, causing cell cycle arrest and apoptosis through activating a number of molecular pathways (12,13). Taxanes are able to drive COX-2 expression, which is followed by increased prostaglandin E_2 (PGE_2) production (14); therefore, a complementary and additive or synergistic effect with COX-2 inhibitors may be expected. Moreover, the response to carboplatin plus docetaxel in Asian patients was reported to be statistically superior to that in Caucasian patients (15).

Based on the abovementioned findings, we projected a prospective phase II trial using carboplatin, docetaxel and a

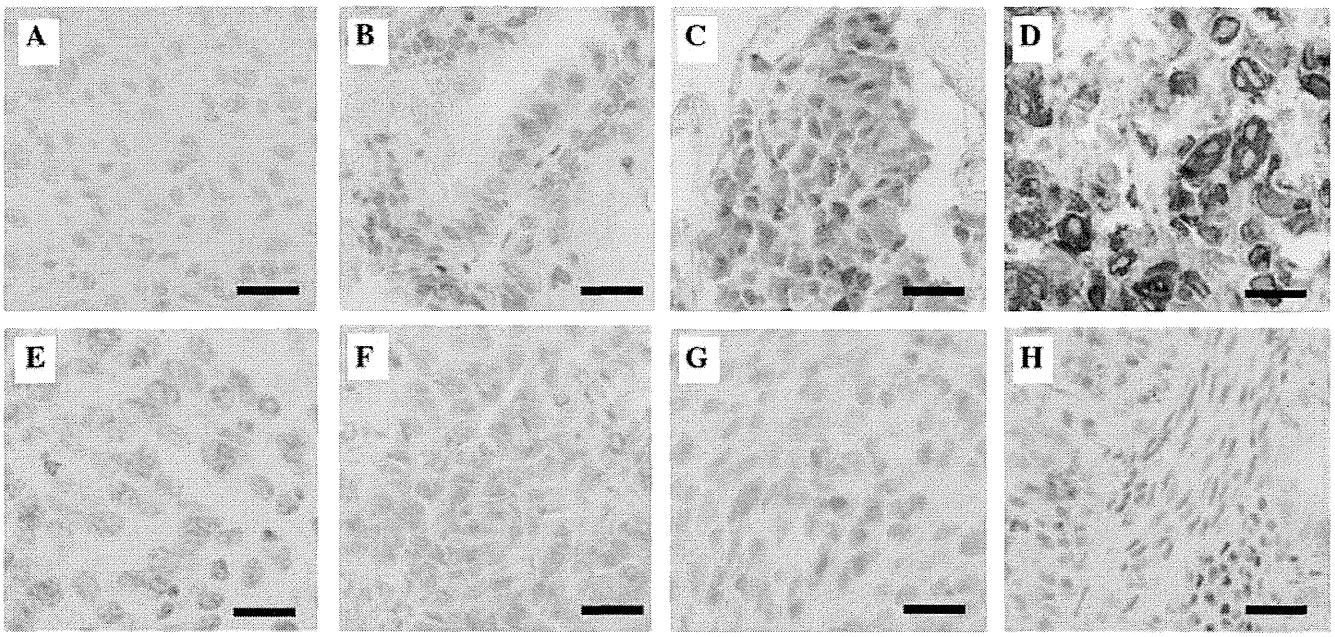

Figure 1. Representative immunohistochemical staining of (A-D) cyclooxygenase-2 and (E-H) p27 in lung cancer tissues obtained from the patients in this study. (A and E) 0, no expression; (B and F) 1+, weak expression; (C and G) 2+, moderate expression; and (D and H) 3+, strong expression. Scale bars, 250 μm.

selective COX-2 inhibitor for patients with advanced NSCLC. We also investigated the p27 and COX-2 expression levels in the tumors, so as to determine the correlation between these molecules and the clinical outcome of the combined treatment.

Materials and methods

Patient characteristics. The eligibility criteria included histologically or cytologically confirmed stage IIIB/IV NSCLC, a patient age of 20-75 years and a life expectancy of >3 months. The patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors, version 1.0, had received no prior chemotherapy or radiotherapy for target lesions and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. The required laboratory criteria were white blood cell (WBC) count >4,000/mm^3, neutrophil count >2,000/mm^3, platelet count >100,000/mm^3, hemoglobin >9.0 g/dl, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <1.5-fold of the upper limit of the normal range (ULN), total bilirubin <1.5 mg/dl and creatinine clearance (CCr) >50 ml/min. The exclusion criteria were active infection or fibrosis on chest X-ray, significant cardiovascular disease, uncontrolled diabetes mellitus or hypertension, peripheral nervous disorders of grade ≥2 according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, active secondary malignancy, central nervous system symptoms due to metastasis, uncontrolled pleural or pericardial effusion, history of severe drug hypersensitivity, recent or current use of non-steroidal anti-inflammatory drugs, pregnancy, or patients deemed inappropriate for the study by the participating physicians.

This study was performed in accordance with the Declaration of Helsinki and all the patients signed an informed consent prior to inclusion. The study protocol was approved by the Institutional Review Board of each participating institution.

Study design and treatment protocol. This was a single-arm prospective phase II study. The dose of carboplatin was determined using the Calvert formula with a target area under the curve (AUC) of 5 mg/ml x min. All the patients received docetaxel (60 mg/m^2) and carboplatin at an AUC of 5 mg/ml x min on day 1 every 3 weeks. Oral meloxicam at a dose of 10 mg daily was administered on days 1-21. We investigated p27 and COX-2 expression levels in tumors by immunohistochemistry (IHC). Dose reduction was permitted in the case of grade 4 neutropenia for 3 consecutive days, febrile neutropenia, or patient-physician's decision. The next course of chemotherapy was postponed in case of bone marrow suppression (WBC count <3,000/mm^3, or neutrophil count <1,500/mm^3, or platelet count <100,000/mm^3), non-hematological events (total bilirubin >1.5 mg/dl, AST >1.5 x ULN, ALT >1.5 x ULN, or CCr <50 ml/min) and any non-hematological grade 2 adverse events. The clinical, hematological and biochemical status was assessed on days 1, 8 and 15 in all the courses. Chest radiographs and computed tomography were performed at least once per month. The toxicities were graded using CTCAE, version 3.0.

IHC. IHC was centrally performed at SRL, Inc. (Tokyo, Japan). First, 5-μm sections of the specimens were deparaffinized and hydrated. For antigen retrieval, the slides were microwaved 4 times in 1 mM EDTA (pH 8.0) for 5 min. For COX-2 detection, staining was performed on an automated immunostainer (Ventana NX system; Ventana Medical Systems, Inc., Tucson, AZ, USA). The Endogenous Biotin Blocking kit (Ventana) was used to reduce non-specific staining caused by endogenous biotin present in the tissues. Subsequently, primary antibody (C295; anti-human COX-2 rabbit IgG polyclonal antibody; IBL Co., Ltd., Nagoya, Japan) diluted 1:25 was used for 30 min at 37°C, followed by biotinylated goat anti-rabbit immunoglobulins (E0432; Dako, Glostrup, Denmark) diluted 1:500 and the 3-3'-diaminobenzidine tetrahydrochloride (DAB) kit (Ventana).

The sections were then counterstained with hematoxylin for 1 min. For p27 detection, following antigen retrieval as described above, endogenous peroxidase activity was blocked by 3% hydrogen peroxidase in phosphate-buffered saline (PBS) for 10 min. The sections were washed in water. After blocking non-specific binding with 10% porcine serum in PBS for 10 min, the sections were incubated with the primary antibody (F-8; anti-human p27 mouse IgG1 monoclonal antibody; Santa Cruz, Dallas, TX, USA) diluted 1:50 in a humid chamber at 4˚C overnight. After washing with water, the sections were incubated with biotinylated rabbit anti-mouse immunoglobulins (E0464) (dilution, 1:500; Dako, Glostrup, Denmark) for 30 min at room temperature, washed in water again and then incubated with peroxidase-conjugated streptavidin (dilution, 1:500; Dako) for 30 min at room temperature. Following an additional wash in water, DAB was applied for 5 min and the sections were counterstained with hematoxylin for 1 min.

All the slides were reviewed by two pulmonary oncologists who were blinded to the clinical information. The slides were scored in a method similar to that previously described (weighted index) (16,17). Five random fields per slide at x200 magnification were evaluated to determine the ratio (%) of stained cells and intensity. The estimated ratios of stained cells were between 0% (0) and 100% (1.0), with intervals at a 10% grade. Intensity was scored using a numerical scale (0, no expression; 1+, weak expression; 2+, moderate expression; and 3+, strong expression, Fig. 1). The index (0-3) was calculated as % positive staining x intensity score.

Statistical analysis. The primary endpoint was overall response rate (ORR), defined as the proportion of patients whose best response was either complete or partial response (PR) in the intent-to-treat (ITT) analysis. Assuming that an ORR of 45.0% in eligible patients would indicate potential usefulness, whereas an ORR of 25.0% would be the lower limit of interest, with α=0.05 and β=0.20, 45 patients were required. The secondary endpoints were safety, time-to-progression (TTP), overall survival (OS), OS rate at 1 year and correlation between OS and the expression level of COX-2 and p27. The TTP and OS were estimated using the Kaplan-Meier method. Log-rank tests were used to evaluate the differences in TTP and OS between patients with positive and those with negative COX-2 and p27 expression, as determined by IHC. The association between the protein levels of COX-2 and p27 was evaluated using the Pearson's product-moment correlation coefficient. The correlation between COX-2 and p27 expression and the response rate was evaluated using the Fisher's exact probability test. The statistical analysis was performed using SPSS software, version 20 (IBM Corporation, Armonk, NY, USA). P≤0.05 was considered to indicate statistically significant differences.

Results

Patient characteristics. Between April, 2005 and July, 2006, 50 NSCLC patients were enrolled from 5 institutions. The patients' baseline characteristics are summarized in Table I. The median age was 65 years (range, 44-78 years), 17 patients were female and 24 had an ECOG PS of 1. One patient did not undergo treatment, due to disease progression after registration. The median number of treatment courses was 3 (range, 0-6).

Table I. Patient characteristics.

	Patients (n=50)	
Characteristics	No.	%
Age, years [median (range)]	65 (44-78)	
Gender		
Female	17	34.0
Male	33	66.0
ECOG PS		
0	24	48.0
1	26	52.0
Histology		
Adenocarcinoma	29	58.0
Squamous cell carcinoma	18	36.0
Large-cell carcinoma	2	4.0
Adenosquamous cell carcinoma	1	2.0
Clinical stage (TNM, version 6)		
IIIA	1	2.0
IIIB	15	30.0
IV	32	64.0
Postoperative recurrence	2	4.0
Courses of chemotherapy		
0	1	2.0
1	5	10.0
2	11	22.0
3	9	18.0
4	19	38.0
5	3	6.0
6	2	4.0

ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis.

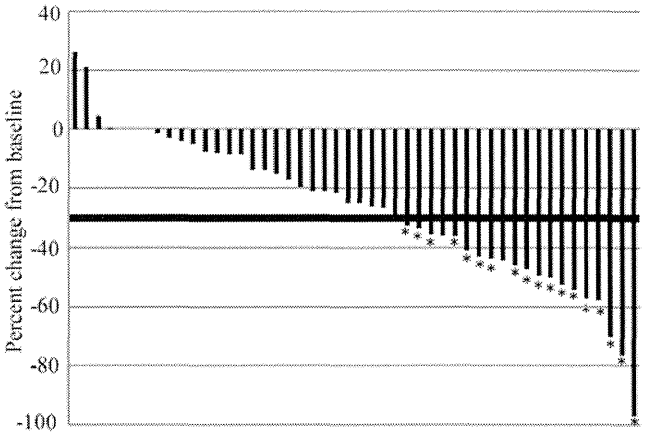

Figure 2. Waterfall plot for the extent of tumor shrinkage. The asterisks represent patients exhibiting a partial response.

Efficacy. A total of 49 patients were evaluable for response to treatment. The majority of the patients achieved tumor shrinkage (Fig. 2). According to the ITT analysis, the ORR

Table II. Objective response (RECIST, version 1.0).

Type of response	No.	%
Number of patients evaluated	50	100.0
Complete response	0	0.0
Partial response	18	36.0
Stable disease	20	40.0
Progressive disease	9	18.0
Not evaluable	3	6.0
Response rate (95% CI)	36.0 (24.1-49.9)	
Disease control rate (95% CI)	76.0 (62.5-85.8)	

RECIST, Response Evaluation Criteria in Solid Tumors; CI, confidence interval.

was 36.0 (95% CI: 24.1-49.9) and the disease control rate (DCR) was 76.0 (95% CI: 62.5-85.8) (Table II). The median follow-up time was 12.9 months (range, 2.1-26.2 months). The TTP and OS were 5.7 months (95% CI: 4.6-6.7) and 13.7 months (95% CI: 11.4-15.9), respectively (Fig. 3). The OS rate at 1 year was 56.0%.

Safety. The incidence of treatment-related adverse events is presented in Table III. The grade 3/4 hematological adverse events were leukopenia (58.0%), neutropenia (80.0%), anemia (16.0%), thrombocytopenia (4.0%) and febrile neutropenia (8.0%). The grade 3/4 non-hematological toxicities were anorexia (12.0%), nausea/vomiting (8.0%), diarrhea (4.0%), fever (4.0%), alopecia (2.0%), neuropathy (2.0%) and myopathy (2.0%). One patient (2.0%) had grade 3 angina pectoris: the patient experienced chest pain on day 3 during the first course of the treatment, which was relieved by immediate infusion of heparin and coronary vasodilator for 6 days; however, the patient's treatment was terminated. Another patient (2.0%) suffered from febrile neutropenia and pneumonia followed by septic shock, requiring treatment with antibiotics and catecholamines on day 12 and developed deep vein thrombosis (DVT) in the left leg on day 26 during the second course of the treatment. The DVT was controlled using heparin followed by warfarin; however, the treatment protocol was discontinued.

Association between expression of p27 and COX-2 and clinical outcome. Tissue samples were obtained from 34 (68.0%) of the 50 patients. Of the 34 samples, 32 were considered adequate for IHC. Of the 32 patients, 2 were not evaluable and one did not undergo treatment after registration. The expression of COX-2 and p27 was tabulated with clinical outcome and cut-off points were established by visual inspection of the data. We did not identify a correlation between the weighted index of COX-2 and that of p27. There was a trend of correlation between the level of COX-2 expression and ORR (50.0% in the high- and 18.2% in the low-COX-2 group; P=0.092) when the cut-off value of the index was 0.2 (Table IV). The level of p27 expression was not associated with ORR (54.5% in the high- and 27.8% in the low-p27 score group; P=0.24). The TTP and OS of the patients with positive and negative COX-2 expression were estimated by the Kaplan-Meier method; however there was no significant difference between the two groups (TTP: 6.0 vs. 4.9 months, P=0.357; and OS: 14.9 vs. 13.9 months; P=0.372, respectively). There was also no significant difference in either TTP or OS between patients whose tumors were positive and those whose tumors were negative for p27 (TTP: 6.0 vs. 5.1 months, P=0.613; and OS: 14.9 vs. 13.4 months, P=0.438, respectively).

Table III. Adverse events (CTCAE, version 3.0).

	Grade		
Adverse events	1-2 (%)	3 (%)	4 (%)
Leukopenia	26.0	50.0	8.0
Neutropenia	6.0	14.0	66.0
Anemia	62.0	10.0	6.0
Thrombocytopenia	30.0	4.0	0.0
Febrile neutropenia	0.0	6.0	2.0
Anorexia	55.0	12.0	0.0
Nausea/vomiting	48.0	8.0	0.0
Diarrhea	18.0	4.0	0.0
Fever	28.0	4.0	0.0
Alopecia	44.0	2.0	0.0
Neuropathy	10.0	2.0	0.0
Myopathy	0.0	2.0	0.0
Angina pectoris	0.0	2.0	0.0
Aphtha	16.0	0.0	0.0
Skin rash	2.0	0.0	0.0
Arthralgia	2.0	0.0	0.0
Thrombosis	2.0	0.0	0.0

CTCAE, Common Terminology Criteria for Adverse Events.

Table IV. Correlation between COX-2 expression and response.

COX-2 IHC index	PR	SD+PD	Total
High	9	9	18
Low	2	9	11
Total	11	18	29

COX-2, cyclooxygenase-2; PR, partial response; SD, stable disease; PD, progressive disease; IHC, immunohistochemistry.

Discussion

In this trial, we investigated the effectiveness and toxicity of COX-2 inhibitors administered with carboplatin plus docetaxel in Japanese NSCLC patients and the association between tumor COX-2 and p27 expression and clinical outcome. There was a trend of correlation between the level of COX-2 expression and ORR. We first attempted to determine how p27 expression, which involves COX-2-independent mechanisms of G0/G1 arrest driven by COX-2 inhibitors, affects patient survival. However, the results revealed no statistical correlation. The

Table V. Previous phase II-III studies of platinum doublet and COX-2 inhibitor in NSCLC.

Design	Author (year)	No. of patients	COX-2 inhibitor	Chemotherapy	Response rate (%)	Median PFS (months)	Median OS (months)	(Refs.)
Phase II	Edelman *et al* (2008)	45	Celecoxib	CBDCA+GEM	NA	4.3[a]	11.8	(23)
	Wang *et al* (2008)	44	Celecoxib	CDDP+GEM CDDP+VNR CDDP+DOC	45.0	6.0	18.0	(24)
	Suzuki *et al* (2009)	44	Meloxicam	CBDCA+PTX	43.0	5.4[b]	15.9	(35)
	This study	50	Meloxicam	CBDCA+DOC	36.0	5.7[b]	13.7	
Phase III	Groen *et al* (2011)	281	Celecoxib	CBDCA+DOC	38.0	4.5	8.2	(21)
		280	Placebo		30.0	4.0	8.2	
	HR					0.8	0.9	
	95% CI					0.6-1.1	0.6-1.2	
	P-value					0.25	0.32	
	Koch *et al* (2011)	158	Celecoxib	3rd generation	36.0	6.1	8.9	(22)
		158	Placebo	Drug + platinum	31.0	6.5	7.9	
	HR					1.01	1.0	
	95% CI					0.77-1.33	0.79-1.26	
	P-value					0.94	0.97	

[a]Failure-free survival. [b]Time-to-progression. COX-2, cyclooxygenase-2; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; OS, overall survival; CBDCA, carboplatin; GEM, gemcitabine; NA, not available; CDDP, cisplatin; VNR, vinorelbine; DOC, docetaxel; PTX, paclitaxel; HR, hazard ratio to placebo; CI, confidence interval.

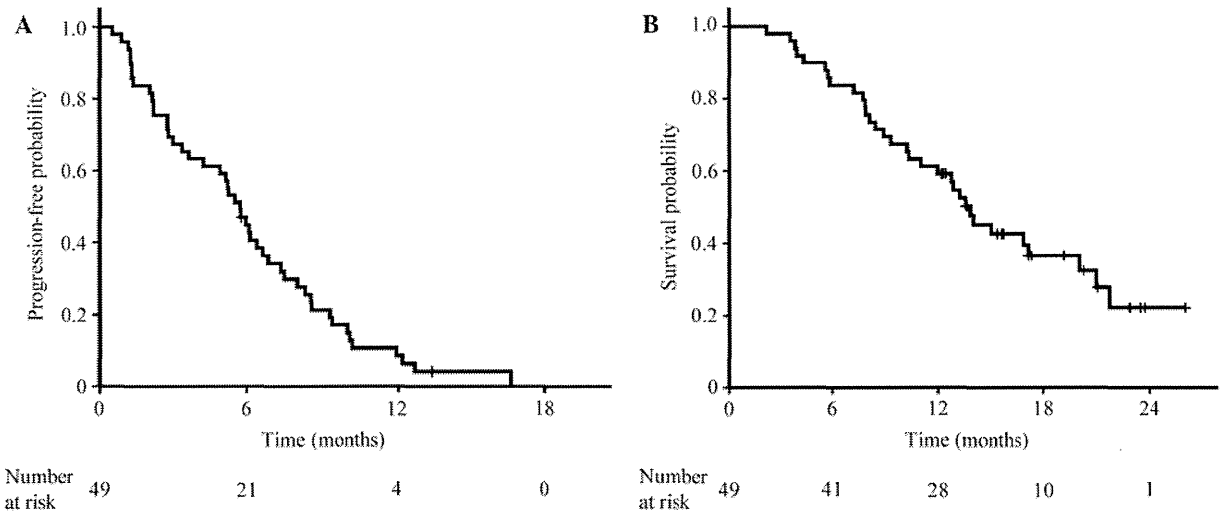

Figure 3. Survival outcomes after treatment. Kaplan-Meier estimates of (A) time-to-progression and (B) overall survival. Vertical bars, censored cases at the data cut-off point.

overall treatment efficacy was favorable, but was not enhanced by COX-2 inhibitors in terms of tumor response (36.0%), OS (13.7 months) and 1-year survival ratio (56.0%). Previous phase II-III trials of docetaxel and carboplatin without COX-2 inhibitors for advanced NSCLC demonstrated that the ORR, OS and 1-year survival rate were 16.0-55.0%, 9.0-13.9 months and 44.0-58.0%, respectively (15,18-20). The incidence of adverse events, such as grade 3/4 neutropenia (80.0%) and febrile neutropenia (8.0%), was similar to those previously reported (51.1-79.0 and 3.3-26.0%, respectively). The frequencies of grade 3/4 myopathy (2.0%) and arthralgia (0.0%) were comparable to or lower compared to those reported by several phase II trials using carboplatin plus docetaxel without a COX-2 inhibitor (3.0-4.0 and 3.0%, respectively) (15,18).

Two recent phase III trials (Table V) (21,22) that used a design identical or similar to that of our study, failed to demonstrate any survival benefit with the addition of a COX-2 inhibitor to chemotherapy in patients with advanced NSCLC. Groen *et al* (21) demonstrated no statistical difference regarding survival between NSCLC patients with tumors

positive and those with tumors negative for COX-2 expression, as determined by IHC.

To elucidate whether COX-2 inhibitors are beneficial for NSCLC patients, we must consider several aspects of COX-2-based strategy based on previous studies (Table V) and reports.

First, there have been no prospective phase III trials with the design of a COX-2 inhibitor or placebo used only in COX-2-positive patients with NSCLC. Groen *et al* (21) investigated the association between COX-2 positivity and progression-free survival (PFS) and OS as a subgroup analysis. A phase II trial (23) demonstrated that prospectively defined subset analysis indicated a survival advantage with a COX-2 inhibitor and chemotherapy in patients with moderate-to-high COX-2 expression. Another group conducted a phase II trial using COX-2 inhibitors combined with platinum-based chemotherapy in 44 previously untreated patients with COX-2-positive advanced NSCLC confirmed by IHC; that study reported promising results, with a median PFS and OS of 6 and 18 months, respectively (24).

Another reason supporting that we should focus on only COX-2-positive patients is the possibility of negative pharmacological effects of COX-2 inhibitors on patients with COX-2-negative tumors. Our results and those of a previous phase II trial (23) suggested that patients who do not express COX-2 may exhibit worse outcomes when treated with COX-2 inhibitors. The inhibition of COX-2 reportedly results in an imbalance between anti- and prothrombotic factors, with a predominance of thromboxane (TX)A_2 at the expense of prostacyclin, which may trigger a series of cardiovascular complications (25). TXA_2-TXA_2 receptor signaling facilitates tumor colonization through interaction of tumor cells with platelets and endothelial cells in the tumor microenvironment (26). TXA_2 is also known to promote tumor metastasis (27). Therefore, it is hypothesized that, by inhibiting COX-2, the COX-1 pathway may become dominant in normal cells, thereby assisting tumor growth in COX-2-negative cells. Other investigators reported that celecoxib treatment induced epithelial-to-mesenchymal transition, which promoted cell invasion and rendered cells resistant to chemotherapy (28). These negative effects may obscure the positive effects in COX-2-expressing patients.

Second, we have not fully pursued the subpopulation benefits for a COX-2 inhibitor on both the clinical and molecular basis. Kozak *et al* (29) found that markedly elevated urinary levels of the major PGE_2 metabolite, which is a downstream signaling molecule of COX-2, were observed in patients with digital clubbing. Patients with high urinary levels of PGE_2 may benefit from COX-2 inhibitors. Another group demonstrated that low pretreatment plasma levels of vascular endothelial growth factor are predictive of a positive effect of celecoxib on survival (30).

The molecular analysis-based selection of therapeutic agents for patients with advanced lung cancer is associated with significant benefits. The identification of epidermal growth factor receptor gene mutations (31) and the anaplastic lymphoma kinase fusion gene (32) contributed to predicting susceptibility to drugs such as gefitinib/erlotinib or crizotinib. The examination of the genetic background of a tumor may be crucial for identifying patients who may benefit from COX-2 inhibitors. Although the genes of the COX pathway are rarely mutated in cancer cells (33), epigenetic alterations, such as DNA methylation, are recurrent events associated with longer recurrence times and improved OS in gastric cancer patients (34). Further investigation is required to determine the association of the genetic and epigenetic deregulation of the COX pathway with clinical outcome in lung cancer.

As shown in Table V, the OS in Asian patients with NSCLC appears to be longer compared to that in non-Asian patients (21-24,35). Pharmacoethnic differences in the response of cancer patients to certain drugs was recently reported (36). However, the diversity of the metabolic action of COX-2 inhibitors among different ethnicities has yet to be elucidated. Thus, identifying such differences may help achieve a better understanding of the molecular mechanism(s) underlying the response to COX-2 inhibitors.

In conclusion, although administered to only 'unselected' patients in a randomized phase III trial that yielded negative results, COX-2 inhibitors may be worth further consideration for the treatment of NSCLC patients.

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