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Konstantinos N. Syrigos · Christopher M. Nutting
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Tumors of the Chest

Biology, Diagnosis and Management

With 115 Figures, 55 in Color and 138 Tables

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Cover Illustration: My Inferno of Hell is a painting by Panos Tzortzinis, one of the most renowned of contemporary Greek painters. An artist who has participated in several domestic and international exhibitions, he was born in Kalamata, Peloponnesus in 1950 and is currently Professor of Art at the Egaleon School of Art. This painting, deriving from Tzortzini's own lung cancer diagnosis, attempts to visually convey his personal thoughts and feelings while undergoing chemotherapy.

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Clinical Trials for Lung Cancer in Progress in Japan

Ikuo Sekine, Yuichiro Ohe, Nagahiro Saijo and Tomohide Tamura

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39.1 Introduction

Lung cancer has been the leading cause of death from cancer in many countries, despite extensive basic research and clinical trials. About 80% of patients with lung cancer have already developed distant metastases, either by the time of the initial diagnosis or by the time recurrence is detected after surgery for local disease. Systemic chemotherapy is the mainstay of lung cancer treatment, although its efficacy is still limited. Therefore, new chemotherapeutic agents continue to be developed against lung cancer [1].

39.2 Drug Approval System in Japan

Since 1955, 23 anticancer drugs have been approved for use against lung cancer in Japan. Of these, 9 were discovered and developed in Japan, including mitomycin, bleomycin, and the topoisomerase I inhibitor irinotecan, and are routinely used all over the world. The Japanese Pharmaceutical Affairs Law (PAL) was enacted in 1948, and was first amended in 1960 to provide for regulations to ensure the maintenance of the quality, efficacy, and safety of drugs and medical devices, and to promote research and development of these medical and pharmaceutical products. Good Clinical Practice was enforced by the Bureau Notification of the Ministry of Health and Welfare of Japan in 1989. In 1996, PAL and its related laws were amended to strengthen Good Clinical Practice, Good Laboratory Practice, Good Postmarketing Surveillance Practice, and standard compliance reviews, conforming to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [2]. In contrast to the laws prevailing in the US and EU, in Japan, marketing approval for anticancer agents can be granted based on reports of the antitumor effects of the new agents in phase II studies. Two independently conducted comparative phase III trials with survival as the endpoint are required after the approval, with at least one of these conducted as a post-marketing sponsored (PMS) trial in Japan [2].

39.3 Recent Clinical Trials for Non-Small-Cell Lung Cancer

Several randomized phase III trials for previously untreated advanced non-small cell lung cancer (NSCLC) have been conducted by Japanese pharmaceutical companies. A three-arm trial of cisplatin + vindesine versus cisplatin + irinotecan versus irinotecan alone conducted on 398 patients with stage IIIB or IV NSCLC between 1995 and 1998 showed that the overall response rate (31%, 43%, and 21%, respectively, $p < 0.001$), but not the overall survival rate (median survival time [MST], 47, 52, and 47 weeks, respectively, $p = 0.099$), was significantly better in the cisplatin + irinotecan arm than in the other two arms [3]. A second trial conducted on 210 patients with advanced NSCLC, comparing cisplatin + vindesine versus cisplatin + irinotecan, showed no statistically significant difference in the overall response rate (22% versus 29%) or survival rate (MST, 50 versus 45 weeks) between the two arms [4]. A randomized phase III trial of docetaxel + cisplatin versus vindesine + cisplatin was conducted between 1998 and 2000 on 305 patients with stage IV NSCLC. Both the overall response rate and the survival rate were significantly superior in the docetaxel + cisplatin arm as compared to the vindesine + cisplatin arm (response rate, 37% versus 21%, re-

spectively, $p<0.01$; MST, 11.3 versus 9.6 months, respectively, $p=0.014$) [5, 6]. After the commercial use of paclitaxel, gemcitabine, and vinorelbine was approved for NSCLC in 1999, a phase III study was conducted to confirm the efficacy and safety of these agents, to fulfill the requirements of PAL. A four-arm randomized phase III study of these agents for NSCLC was conducted in cooperation with three pharmaceutical companies. The four arms consisted of cisplatin (80 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1, 8, and 15) administered every 4 weeks as the reference arm; carboplatin (area under the curve [AUC] 6 on day 1) + paclitaxel (200 mg/m^2 on day 1) administered every 3 weeks; cisplatin (80 mg/m^2 on day 1) + gemcitabine (1,000 mg/m^2 on days 1 and 8) every 3 weeks; and cisplatin (80 mg/m^2 on day 1) + vinorelbine (25 mg/m^2 on days 1 and 8) administered every 3 weeks. Of a total of 602 patients registered from 44 institutes in Japan between 2000 and 2002, 581 were assessable for response, toxicity, and survival. The overall response rates in the four arms were 31%, 32%, 30%, and 33%, respectively, and the MST was 14.2, 12.3, 14.8, and 11.4 months, respectively. Non-inferiority of the three experimental arms as compared to the reference arm was not demonstrated in this study [5, 6].

Docetaxel monotherapy is the standard second-line treatment for NSCLC patients, based upon the demonstration of improved survival and quality of life in phase III studies [7, 8]. The Japan Clinical Oncology Group (JCOG) conducted a phase III trial (JCOG0104) to evaluate the efficacy and toxicity of gemcitabine combined with docetaxel in NSCLC patients with a history of prior platinum-based chemotherapy. The chemotherapeutic regimens compared in this study consisted of docetaxel alone (60 mg/m^2 on day 1) or docetaxel (60 mg/m^2 on day 8) + gemcitabine (800 mg/m^2 on days 1 and 8), repeated every 21 days until disease progression, with a planned sample size of 142 patients per arm. Between January 2002 and April 2003, 65 patients were accrued for each arm. However, this trial was terminated early because of the unexpectedly high incidence of interstitial lung disease (ILD) and three treatment-related (all due to ILD) deaths (5%) in the docetaxel + gemcitabine arm. While the incidence of grade 3–4 neutropenia and febrile neutropenia was similar in both the arms, the incidence of dyspnea (23% versus 14%) and ILD (21% versus 2%) was higher in the docetaxel + gemcitabine arm [9]. A randomized, double-blind, parallel-group, international, multicenter trial of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was conducted in patients with advanced NSCLC with recurrent or refractory disease following therapy with one or two chemotherapeutic regimens, at institutes in Europe, Australia, South Africa, and Japan. Patients were randomized to receive either 250 or 500 mg/day gefitinib using blinded tablets, until disease progression, intolerable toxicity, or withdrawal of consent. Between October 2000 and January 2001, 102 patients were enrolled from 19 institutes in Japan. The objective tumor response rate in the Japanese patients was 28% in both the 250- and the 500-mg/day arms. Thus, there was no difference in the objective response rate depending on the dose of gefitinib, although the incidence of toxicities, including rash, diarrhea, liver damage, and nausea, was relatively lower in the 250-mg/day arm [10]. A randomized, open-labeled phase III trial of second-line chemotherapy with docetaxel versus gefitinib in patients with advanced NSCLC previously treated with platinum-based chemotherapy is in progress in Japan as a PMS trial,

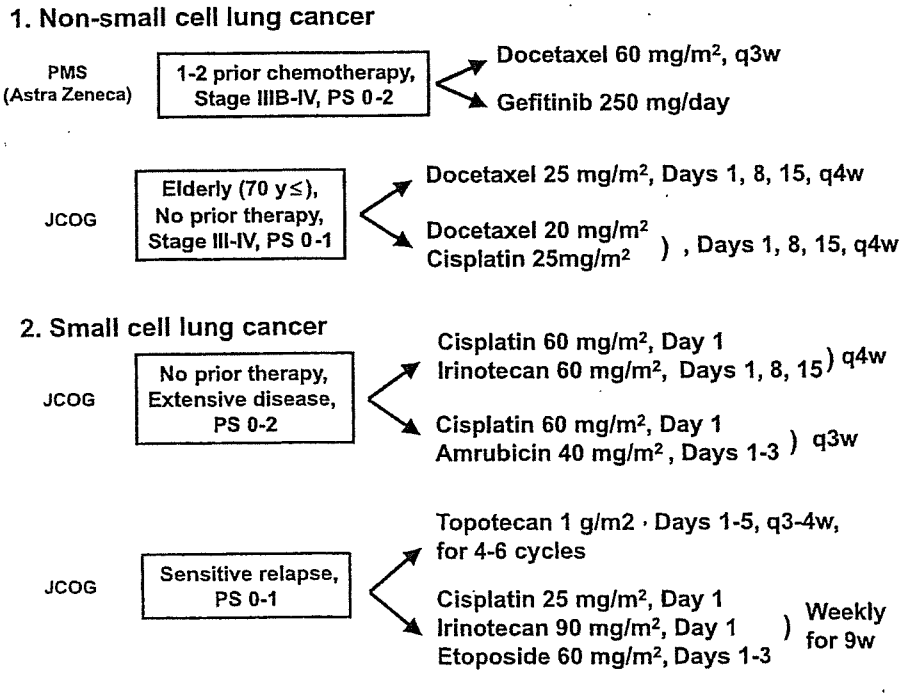

Fig. 39.1. Phase III trials in progress or being planned in Japan. *PMS* Post-marketing sponsored, *JCOG* Japan Clinical Oncology Group

since December 2003. The projected accrual for this study is a total of 484 patients (242 patients per treatment arm) (Fig. 39.1).

Monotherapy with a third-generation cytotoxic agent is widely accepted for the treatment of advanced NSCLC in the elderly, after demonstration of the survival benefit of vinorelbine over standard supportive care alone, without deterioration of the quality of life, in a phase III trial [11]. The West Japan Thoracic Oncology Group (WJTOG) is conducting a phase III trial (WJTOG 9904) of docetaxel (60 mg/m^2 on day 1) versus vinorelbine (25 mg/m^2 on days 1 and 8) administered every 3 weeks for advanced NSCLC in patients aged 70 years or older with no prior history of chemotherapy, a performance status of 0–2, and adequate organ function, as indicated by routine blood counts and blood chemistry, and electrocardiography. The projected sample size for this trial is 90 patients for each arm, and patient accrual for this study has recently been completed.

There are limited data to support the use of platinum-based combination chemotherapeutic regimens in patients over 70 years of age, although platinum doublet is standard treatment for younger patients. A retrospective analysis of 401 patients 65 years of age or older in a large phase III trial of docetaxel + cisplatin versus docetaxel + carboplatin versus vinorelbine + cisplatin revealed no significant differences in the therapeutic outcomes based on the age, although a moderately higher incidence of grade 3–4 asthenia, infection, pulmonary toxicities, diarrhea, and sensory neurotoxicity was noted in the elderly patients [12]. A phase I and a phase II study showed that a combination of cisplatin and docetaxel administered as three consecutive weekly infusions was safe and effective in elderly patients with advanced NSCLC [13, 14]. Based on these data, a JCOG phase III trial of weekly docetaxel versus weekly docetaxel + cisplatin (JCOG0207) is under way (Fig. 39.1). The primary endpoint of this study is the overall survival of the patients treated with these regimens. The secondary endpoints are the response rate, progression-free survival, toxicity, and symptom score. Eligibility includes stage IV or IIIB disease, no history of previous chemotherapy, performance status of 0 or 1, age 70 years or older, and adequate organ functions. The chemotherapeutic regimens consisted of docetaxel (25 mg/m^2) administered on days 1, 8, and 15 every 4 weeks, or docetaxel (20 mg/m^2) + cisplatin (25 mg/m^2) administered on days 1, 8, and 15 every 4 weeks. The projected accrual for this study is a total of 230 patients (115 patients per treatment arm).

39.4 Recent Clinical Trials for Small-Cell Lung Cancer

The JCOG conducted a phase III study of cisplatin (60 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1, 8, and 15) administered every 4 weeks versus cisplatin (80 mg/m^2 on day 1) + etoposide (100 mg/m^2 on days 1, 2, and 3) administered every 3 weeks for untreated extensive small-cell lung cancer (E-SCLC) (JCOG9511). The projected sample size for this study was 230 patients (115 patients per treatment arm), however, enrollment was stopped early because of a statistically significant difference in the survival observed between the two treatment arms on interim analysis. In this interim analysis, 154 patients were randomized to the two treatments, 77 into each arm. The overall response rate and survival were significantly better in the cisplatin + irinotecan group (response rate, 84% versus 68%, respectively, $p = 0.02$; MST, 12.8 versus 9.4 months, respectively, $p = 0.002$) [15]. Based on these observations, the combination of cisplatin + irinotecan is used as the standard chemotherapeutic regimen for E-SCLC in Japan. A three-drug combination of cisplatin, irinotecan, and etoposide was investigated. The maximum tolerated dose of each of the three drugs was determined in phase I studies using two different schedules: a weekly (JCOG9507) and a 4-weekly (JCOG9512) schedule. The antitumor effects of these regimens were evaluated in a randomized phase II study (JCOG9902DI) [16]. The weekly arm consisted of cisplatin (25 mg/m^2 on day 1 at weeks 1–9), irinotecan (90 mg/m^2 on day 1 at weeks 1, 3, 5, 7, and 9), and etoposide (60 mg/m^2 on days 1–3 at weeks 2, 4, 6, and 8), administered with granulocyte colony-stimulating factor (G-CSF) support. The 4-weekly arm consisted of cisplatin (60 mg/m^2 on day 1), irinotecan (60 mg/m^2 on days 1, 8, and 15), and etoposide (50 mg/m^2 on days 1–3) administered with G-CSF support. From August 1999 to October 2000, 30 patients were entered in each of the two treatment arms of this study. Although 70% of all the patients received full cycles of chemotherapy in both arms, treatment delay in the weekly arm and skipping of irinotecan on day 15 in the 4-weekly arm were common because of toxicity. The complete and partial response rates and the MST were 7%, 77%, and 8.9 months, respectively, in the weekly arm, and 17%, 60%, and 12.9 months, respectively, in the 4-weekly arm. Since no overall survival benefit was obtained with the weekly schedule, and the dose of irinotecan on day 15 frequently needed to be skipped in the 4-weekly schedule, a 3-week schedule with irinotecan administered only on days 1 and 8 every 3 weeks might be appropriate for subsequent trials. A randomized phase II trial of cisplatin (60 mg/m^2 on day 1) + irinotecan (60 mg/m^2 on days 1 and 8) versus the same three-drug combination of cisplatin and irinotecan combined with etoposide (50 mg/m^2 on days 1–3) administered

every 3 weeks with G-CSF support in patients with previously untreated E-SCLC is in progress.

Amrubicin (SM-5887) is an entirely synthetic anthracycline that has been shown to possess topoisomerase II inhibitory activity. It has been shown to exert more potent antitumor activity than doxorubicin against various experimental tumors and human tumor xenografts in mice, without any cardiotoxicity. A phase II study of single-agent amrubicin using a schedule of 45 mg/m^2 administered on days 1–3 every 3 weeks yielded an overall response rate of 76%, a complete response rate of 9%, and an MST of 11.7 months in 33 previously untreated E-SCLC patients [17]. The recommended dose of amrubicin when combined with cisplatin was determined to be 40 mg/m^2 on days 1–3 every 3 weeks, and the response rate and MST for E-SCLC patients receiving this combination were 88% and 13.6 months, respectively [18]. The next JCOG phase III trial for this patient population should be of a combination of cisplatin + amrubicin versus cisplatin + irinotecan (Fig. 39.1).

Despite a high response rate to chemotherapy, the majority of SCLC patients eventually develop recurrent disease. At the time of recurrence, the tumor is broadly resistant to second-line chemotherapy and death occurs within a few to several months [19]. Thus, there is need for further development of effective salvage chemotherapy. We conducted a phase II study of cisplatin (25 mg/m^2) administered weekly for 9 weeks, etoposide (60 mg/m^2) administered for 3 days on weeks 1, 3, 5, 7, and 9, and irinotecan (90 mg/m^2) administered on weeks 2, 4, 6, and 8, with G-CSF support, in patients with sensitive relapsed SCLC [20]. Since the drug dose and treatment schedule can be easily modified according to the patient condition in the weekly regimen, it is considered that this regimen may be the most suitable for relapsed SCLC patients, who usually present with severe hematological toxicities during salvage chemotherapy because of poor bone marrow reserve. In a total of 40 patients registered, the overall response rate was 78% with 5 complete responses and 26 partial responses, and the MST was 11.8 months. Grade 3–4 neutropenia and thrombocytopenia were observed in 73% and 33% of the patients, respectively, and the non-hematological toxicities were mild and transient in all the patients. The JCOG is planning a phase III study to compare the efficacy of this regimen with that of topotecan monotherapy in sensitive relapsed SCLC patients (Fig. 39.1).

At diagnosis, 25–40% of patients with SCLC are 70 years old or older, and this percentage is expected to increase with the growing population of geriatric patients. Carboplatin is especially useful for the elderly because only minimum hydration of the patients is required, its non-hematological toxicity is mild, and the dose can be adjusted according to the patient's creatinine clearance [21]. The JCOG evaluated the toxicity and efficacy of this drug in a phase II study (JCOG9409), and observed grade 4 neutropenia and thrombocytopenia in 44% and 12% of the patients, respectively, and complete response and partial response in 6% and 69% of the patients, respectively [22]. We started a large phase III trial in 1998, to compare the clinical efficacy of etoposide (80 mg/m^2 on days 1–3) + carboplatin (AUC = 5) versus etoposide (same dose) + cisplatin (25 mg/m^2 on days 1–3) in elderly patients with SCLC (JCOG9702). The sample size was 220 patients (110 patients for each arm), and registration was completed in February 2004.

39.5 New Agents for the Treatment of Lung Cancer

The development of oral preparations of 5-fluorouracil (5-FU) began in Japan in 1971, based on the finding that 5-FU acts in a time-dependent manner and on the possibility of treating patients on an outpatient basis, without deterioration of the quality of life, when drugs can be administered orally. S-1 (Taiho Pharmaceutical) is a novel oral fluoropyrimidine derivative consisting of tegafur, a prodrug of 5-FU, and two modulators, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1 [23]. CDHP enhances the serum 5-FU concentrations by competitive inhibition of dihydropyrimidine dehydrogenase, an enzyme responsible for 5-FU catabolism. Oxo reduces 5-FU-induced diarrhea by inhibiting orotate phosphoribosyltransferase, a phosphoenzyme for 5-FU in gastrointestinal tissue. In a phase I trial, the maximum tolerated dose of S-1 was 75–100 mg/body, and the dose-limiting toxicity was myelosuppression. In a phase II trial of S-1 administered orally at approximately 40 mg/m^2 twice a day for 28 days followed by a 2-week rest period in 59 advanced NSCLC patients without prior history of chemotherapy, the response rate was 22% and the MST was 10.2 months, and the incidence of toxicity was relatively low, including grade 3–4 neutropenia in 7%, thrombocytopenia in 2%, diarrhea in 9%, and stomatitis in 2% of the patients [24]. A combination of S-1 and cisplatin was evaluated in a phase II trial for locally advanced and metastatic NSCLC, in which S-1 was administered orally (40 mg/m^2, twice daily) for 21 consecutive days and cisplatin was administered intravenously (60 mg/m^2 on day 8), and this schedule was repeated every 5 weeks. An overall response rate of 47% and MST of 11 months were obtained, with a mild toxicity profile, including grade 3–4 neutropenia in 29%, grade 3 anorexia in 13%, vomiting in 7%, and diarrhea in 7% of the patients [25]. This drug was approved for use in cases of advanced NSCLC by the Ministry of Health, Labor and Welfare of Japan in December 2004, on condition that a phase III trial of S-1 combined with platinum be conducted for advanced NSCLC patients with a reference arm of the standard regimen for this disease.

Several antifolates have been evaluated for the treatment of NSCLC, but none has as yet gained recognition as a useful drug in standard clinical practice. Pemetrexed (LY231514; Eli Lilly Japan) is a novel antifolate with multiple intracellular targets, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase, all key folate enzymes involved in the de novo synthesis of purines and pyrimidines [26]. The recommended dose of pemetrexed from early phase I trials is 600 mg/m^2 administered every 3 weeks, and the dose-limiting toxicity was myelosuppression [27]. Phase II studies conducted with this drug at the dose of 500 mg/m^2 yielded response rates of 15–23% in untreated patients and 9% in previously treated patients with advanced NSCLC [28, 29]. A phase III trial of pemetrexed versus docetaxel as a second-line chemotherapy for NSCLC showed that this drug had the same antitumor activity as docetaxel, but with less toxicity [30]. Because folic acid and vitamin B_{12} supplementation was found to decrease the toxicity of this agent [31], a Japanese phase I trial of the drug was conducted with such vitamin supplementation [32]. In a total of 31 patients (19 with NSCLC, 7 with malignant pleural mesothelioma, 2 with thymoma, 1 with rectal cancer, and 2 others), grade 3 neutropenia was observed in 4 patients, elevated liver transaminase levels in 2 patients, and skin rash in 1 patient, and the recommended dose of pemetrexed was determined to be 1,000 mg/m^2 every 3 weeks. The pharmacokinetic profile of pemetrexed with vitamin supplementation in Japanese patients was essentially similar to that in western patients, with or without vitamin supplementation. In a total of 20 patients who were evaluable for antitumor activity, a partial response was observed in 4 of the 13 patients with NSCLC, and 1 of 2 patients with thymoma. A phase II trial of this drug in previously treated cases of NSCLC is under way in Japan.

Erlotinib (Chugai Pharmaceutical) is another selective inhibitor of EGFR tyrosine kinase sharing a common chemical backbone with gefitinib. Erlotinib was consistently twice as potent as gefitinib in preclinical studies, from cell-free systems to in vivo toxicity and efficacy studies [33]. At the dose of 150 mg, the recommended dose for phase II trials, the plasma AUC of erlotinib was higher by one order of magnitude than that of gefitinib administered at the dose of 250 mg/day [33]. The response rate of erlotinib in phase II trials in the USA was 12% in patients with NSCLC and 26% in patients with bronchoalveolar carcinoma. Phase III trials of standard platinum-based doublet with erlotinib versus placebo in patients with stage IIIB or IV NSCLC (TALENT and TRIBUTE) failed to show any survival benefit of erlotinib over placebo in a whole patient population [34]. A Japanese phase I trial of erlotinib was conducted in 11 patients with NSCLC, 3 patients with colon cancer, and 1 patient with head and neck cancer, using a dose in the range 50–150 mg/day [35]. The toxicity profile was mild, with grade 1–2 skin rash in 87%, grade 1 diarrhea in 53%, and grade 1–2 elevation of liver transaminases in 40% of patients, except for 1 patient who developed fatal ILD following treatment with 100 mg/day erlotinib. The C_{max} increased in a dose-related manner, but there was no clear trend in the AUC. A partial response was observed in 4 (36%) of the 11 NSCLC patients. A phase II trial in previously treated patients with NSCLC is in progress.

Vascular endothelial growth factor (VEGF) is a potent and specific mitogen for endothelial cells that activates the angiogenic switch in vivo through binding to two distinct receptors on endothelial cells: Flt-1 (VEGFR-1) and Flk-1/KDR receptor (VEGFR-2). Enhanced expression of VEGF is generally correlated with increased neovascularization within the tumor [36]. ZD6474 (AstraZeneca) is an orally bioavailable, small-molecule VEGFR-2 tyrosine kinase inhibitor that also possesses activity against the EGFR tyrosine kinase [37]. Oral administration of ZD6474 to athymic mice bearing various established human tumor xenografts produced a dose-dependent regression of the tumors in all the cases [37]. In addition, ZD6474 inhibited the growth of tumors resistant to EGFR inhibitors [38]. A phase I trial of ZD6474 in 18 Japanese patients with solid tumors refractory to standard therapy showed that ZD6474 was well tolerated when administered at the dose of 100–300 mg/day, with common toxicity, including skin rash in 14, asymptomatic QTc prolongation in 11, diarrhea in 10, and hypertension in 7 patients [39]. The C_{max} and AUC of ZD6474 increased linearly with the dose, and the terminal half-life was long, ranging from 72 to 167 h (median 96 h). The dose level of 100–300 mg/day yielded trough concentrations of the non-protein-bound drug of 0.08–0.31 μmol/l in 10 patients, which was over the IC_{50} (0.04 μmol/L) of ZD6474 for VEGFR-2. Preliminary suggestion of tumor regression was observed in 4 out of 9 patients with NSCLC. A phase II trial in advanced NSCLC patients with a history of prior chemotherapy is in progress in Japan.

Since 1995, the quality of clinical trials has improved remarkably in Japan, and large-scale phase III trials have been conducted with the support of the JCOG, WJTOG, and Japanese pharmaceutical companies:

1. Molecular-target drugs, including gefitinib, erlotinib, and ZD6474, have been evaluated in phase II–III trials of NSCLC in Japan.
2. Amrubicin, a new anthracycline, is promising for the treatment of SCLC, and phase III trials are being planned.

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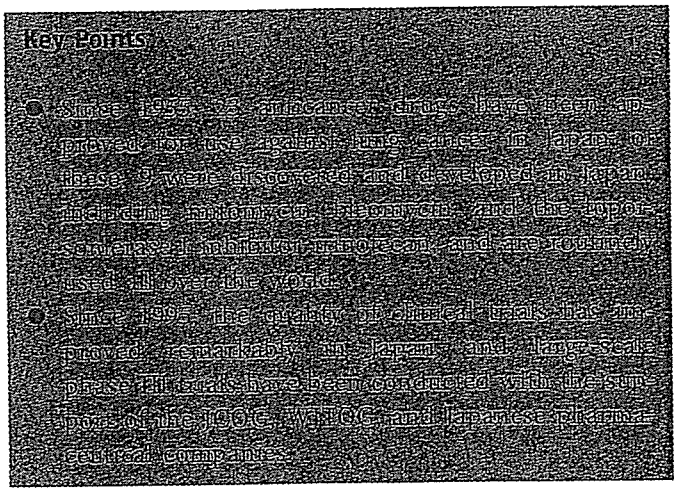

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Pleural Lavage Cytology Before and After Lung Resection in Non-Small Cell Lung Cancer Patients

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Background. The aim of this study was to analyze on a multivariate basis the prognostic significance of pre-resection and post-resection pleural lavage cytologies in surgically resected primary non-small cell lung cancer (NSCLC) patients, in relation to pathologic TNM factors in a large cohort of almost 1,200 patients.

Methods. From August 1992 through March 2001, pleural lavage cytology (PLC) was performed in 1,214 NSCLC patients without pleural effusion or dissemination undergoing pulmonary resection. The cytologic evaluation was classified into three categories: negative, suggestive, and positive. To investigate the impact on patient survival, PLC results were analyzed with conventional clinicopathologic factors.

Results. Definitive pre-resection PLC result was obtained in 1,194 patients and 38 had a positive result. The 5-year survival rates were 27% if pre-resection PLC was positive and 71% if negative. Of 1,198 patients 54 had a positive post-resection PLC result. The 5-year survival rates were 10% if post-resection PLC was positive and 73% if negative. On multivariate analysis, post-resection PLC was an independent prognostic factor as significant as established clinicopathologic factors.

Conclusions. Pre-resection and post-resection PLC should be recognized as an essential prognostic factor and should be performed in NSCLC patients without pleural effusion and dissemination. Post-PLC, compared with pre-PLC, had a greater and independent impact on survival and needs to be incorporated in the pathologic staging of NSCLC in the future.

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Pleural lavage cytology (PLC) has been reported to be a possible prognostic factor in patients with resected non-small cell lung cancer (NSCLC). However, many of the reports are that only PLC immediately after thoracotomy, before lung resection, (pre-PLC) has been studied in detail. The pre-PLC impact on patient outcome has been studied, chiefly, on a univariate basis and has not been studied in relation to the conventional pathologic TNM by multivariate analysis. Although pre-PLC has been reported to be a poor prognosis predictor, a positive result is currently not recognized as equivalent to T4 or a factor indicating incomplete resection. Although PLC after radical NSCLC resection, before chest closure, (post-PLC) has also been studied, significance of post-PLC remains controversial. Higashiyama and associates [1] performed pre-PLC and post-PLC in 325 lung cancer patients, but neither pre-PLC nor post-PLC results were an independent prognostic factor. Dresler and associates [2], who reported the pre-PLC and post-PLC analysis in 137 patients, stated that the 3-year survival rate was significantly better in negative post-PLC patients than in positive patients. We thought further analyses on post-PLC were needed. In the present study, we analyzed both pre-PLC and post-PLC on a multivariate basis, in relation to pathologic TNM factors in a large cohort of almost 1,200 patients.

Material and Methods

From August 1992 through March 2001, a total of 1,387 patients underwent surgical resection for primary NSCLC at the National Cancer Center Hospital East. Intraoperative PLC, which was approved for this observational study by the institutional review board, was prospectively performed in all patients without pleural effusion and dissemination, totaling 1,214 patients, and all were enrolled in this study. As the largest sample size for PLC study was 1,000 before this study, we aimed at accruing well more than 1,000 patients before analysis. Preoperative evaluation included a detailed history, physical examination, bronchoscopy, contrast-enhanced computed tomography (CT) of the chest, and distant metastasis screening (bone, brain, liver, and adrenals). Histologic typing was determined according to the World Health Organization classification [3]. Disease stages were determined based on the TNM classification of the International Union Against Cancer [4]. Immediately after

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thoracotomy, the pleural cavity was carefully washed with 500 mL physiologic saline before any pulmonary parenchyma manipulation. A sample of 50 mL was retrieved for cytologic evaluation (pre-PLC). We performed lung resection (segmentectomy or greater) and complete mediastinal lymph node dissection in 1,199 patients, and lung resection and mediastinal lymph node sampling in 15 patients. Before chest closure, a pleural cavity lavage sample was also retrieved (post-PLC) in the same fashion as pre-PLC. Samples were centrifuged at 1,500 rpm for 5 minutes. The sediment was stained using Papanicolaou's methods. A single cytologist blinded to the clinical-pathologic information evaluated the specimen and classified it into three categories: Papanicolaou classes I and II as negative, class III as suggestive, and classes IV and V as positive. In the survival analyses, we studied only cases with definitive cytologic diagnoses, excluding Papanicolaou class III. To investigate the impact on patient survival, the following conventional clinicopathologic factors were reviewed and analyzed: age, gender, smoking index (< 400 vs ≥ 400), serum carcinoembryonic antigen (CEA) level (< 5.0 mg/mL vs ≥ 5.0 mg/mL), clinical T factor (cT: cT2-4 vs cT1), clinical lymph node status (cN: mediastinal node involvement as cN2 vs less extensive as cN0-1), histologic type of tumor (adenocarcinoma versus others), pleural involvement of surgical (sP0-1 vs sP2-3) and pathologic finding (p0 vs p1-3), lymphatic invasion (positive versus negative), vascular invasion (positive versus negative), pathologic N status (pN: pN2-3 vs pN0-1), degree of fibrotic scarring (scar grade 1-2 vs grade 3-4), nuclear atypia (grade 1 or 2 vs grade 3), mitotic activity (mitotic index 1 or 2 vs 3), and surgical resection completeness (incomplete versus complete). Complete resection was defined as negative surgical margin and no highest mediastinal lymph node involvement. Incomplete resection was defined as positive surgical margin or highest mediastinal lymph node involvement. The smoking index was defined as the product of the number of cigarettes smoked per day and the number of years of smoking. We defined cN2 as mediastinal lymph node(s) greater than 1.0 cm in the shortest dimension on preoperative conventional CT. Pleural involvement was classified according to the Japan Lung Cancer Society criteria: p0; tumor did not extend beyond the elastic pleural layer, p1; tumor invaded the visceral pleura elastic layer but was not exposed on the pleural surface, p2; tumor was exposed on the pleural surface and p3; tumor invaded the parietal pleura or chest wall. Surgeons determined pleural involvement (sP factor) macroscopically before resection. Pathologic pleural involvement (p factor) were diagnosed on the resected specimens by a single pathologist blinded to the surgeons' findings [5]. Lymphatic invasion and vascular invasion indicated tumor cells identifiable in the lymphatic and vascular vessel lumen, respectively. Scar grade was classified into 4 grades: grade 1; tumor had foci of alveolar collapse with resulting condensation of elastic fibers but no or minimal fibroblastic tissue with collagen, grade 2; tumor had fibroblastic tissue with a small amount of collagen fibers, grade 3; tumor had fibroblastic tissue with moderate or abundant amount of collagen fibers, and grade 4; tumor showed hyalinization [6]. Nuclear atypia categorization was based on the most atypical nuclei on sections and divided into 3 grades as follows: grade1; nuclei that were uniform in size and equal to or only slightly larger than those of reactive type II alveolar epithelial

Table 1. Patient Characteristics (n = 1,214)

Characteristics	Results	
Gender		
Male	781	(64)
Female	433	(36)
Histology		
Adenocarcinoma	792	(65)
Squamous cell carcinoma	284	(23)
Others	138	(12)
Clinical T factor		
T1	593	(49)
T2	490	(40)
T3	111	(9)
T4	20	(2)
Clinical N factor		
N0	1,005	(83)
N1	116	(10)
N2	92	(8)
N3	1	(<1)
Clinical stage		
IA	550	(45)
IB	376	(31)
IIA	17	(1)
IIB	129	(11)
IIIA	113	(9)
IIIB	24	(2)
IV	5	(<1)
Pathologic T factor		
T1	543	(45)
T2	434	(36)
T3	126	(10)
T4	111	(9)
Pathologic N factor		
N0	801	(66)
N1	204	(17)
N2	202	(17)
N3	7	(1)
Pathologic stage		
IA	438	(36)
IB	256	(21)
IIA	51	(4)
IIB	147	(12)
IIIA	196	(16)
IIIB	113	(9)
IV	13	(1)

(Numbers in parentheses are percentages)

Table 2. Pre-PLC Result and Clinicopathologic Characteristics

Factors	Pre-PLC (n = 1,194)		P Value
	Positive (n = 38)	Negative (n = 1,156)	
Age	63	63	0.740
Gender			
Male	25	746	
Female	13	410	0.873
Treatment modality (resection type)			
Lobectomy	34	1,049	
Pneumonectomy	1	64	0.177
Limited resection	3	43	(limited resection vs others)
Pathologic stage			
I	16	667	
II	3	193	0.056
III	19	283	(stage I vs others)
IV	0	13	
Histology			
Adenocarcinoma	26	751	
Squamous cell carcinoma	6	274	0.660
Large cell carcinoma	3	47	(adenocarcinoma vs others)
Other	3	84	
Pathologic pleural involvement			
p0	11	754	
p1–3	27	402	<0.001
Pathologic N status			
N0	17	774	
N1–3	21	382	0.041
Lymphatic invasion			
Positive	27	481	
Negative	11	675	<0.001
Vascular invasion			
Positive	30	633	
Negative	8	523	0.003
Resection completeness			
Complete	28	1,067	
Incomplete	10	89	<0.001
Scar grade			
1–2	0	191	
3–4	35	844	0.001
NA	3	121	
Nuclear atypia			
1–2	15	432	
3	20	607	0.863
NA	3	117	
Mitotic index			
1–2	26	813	
3	9	226	0.539
NA	3	117	

NA = data not available.

cells, grade 2; nuclei that were uniform in size and up to twice the size of those of reactive type II alveolar epithelial cells, and grade 3; presence of giant tumor cells. Mitotic index was classified into three grades based on the findings of several sections: index 1; up to 5 mitotic cells per 10 high-power fields (HPF), index 2; 6–15 mitotic cells per 10 HPF, and index 3; greater than 15 mitotic cells per 10 HPF [7]. The length of survival was defined as the interval in months between the day of surgical intervention and the date of death due to

Table 3. Post-PLC Results and Clinicopathologic Characteristics

Factors	Post-PLC (n = 1,182)		
	Positive (n = 54)	Negative (n = 1,128)	*p* Value
Age	61	63	0.363
Gender			
Male	37	725	
Female	17	403	0.524
Treatment modality (resection type)			
Lobectomy	48	1,026	
Pneumonectomy	2	63	0.129
Limited resection	4	39	(limited resection vs others)
Pathologic stage			
I	7	673	
II	3	191	<0.001
III	42	253	(stage I vs others)
IV	2	11	
Histology			
Adenocarcinoma	41	731	
Squamous cell carcinoma	4	270	0.094
Large cell carcinoma	4	46	(adenocarcinoma vs others)
Other	5	81	
Pathologic pleural involvement			
p0	26	732	
p1–3	28	396	0.019
Pathologic N status			
N0	10	776	
N1–3	44	352	<0.001
Lymphatic invasion			
Positive	43	463	
Negative	11	665	<0.001
Vascular invasion			
Positive	41	614	
Negative	13	514	0.002
Resection completeness			
Complete	25	1,001	
Incomplete	29	127	<0.001
Scar grade			
1–2	3	186	
3–4	47	821	0.022
NA	4	121	
Nuclear atypia			
1–2	18	423	
3	32	588	0.465
NA	4	117	
Mitotic index			
1–2	42	790	
3	8	221	0.382
NA	4	117	

NA = data not available.

any cause or the last follow-up. An observation was censored at the last follow-up when the patient was alive or lost to follow-up. The survival rates were calculated by the Kaplan-Meier method [8] and univariate analyses were performed by means of the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model [9]. Forward and backward stepwise procedures were used to determine the combination of prognostic factors (StatView: version 5.0; SAS Institute, Inc, Cary, NC). A *p*

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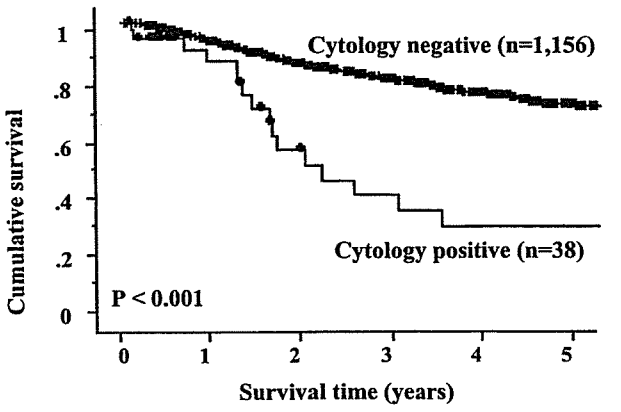
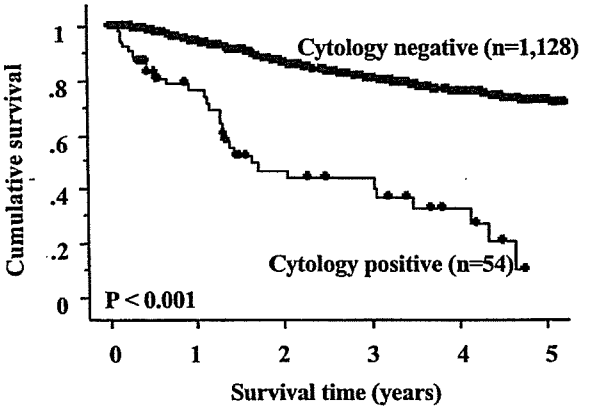


Negative	1156	903	692	528	369	238
Positive	38	21	10	7	5	5

Patients at risk

Fig 1. Survival curves of patients according to pre-PLC results. The 5-year survival rate was 27% for positive pre-PLC patients and was significantly worse (71%) for negative pre-PLC patients. The crosses indicate censored cases at the respective points. (PLC = pleural lavage cytology.)



Negative	1128	888	686	527	417	334
Positive	54	33	16	13	6	0

Patients at risk

Fig 2. Survival curves of patients according to post-PLC results. The 5-year survival rate was 10% for positive post-PLC patients and was significantly worse (73%) for negative post-PLC patients. The crosses indicate censored cases at the respective points. (PLC = pleural lavage cytology.)

value less than 0.05 was taken to indicate a statistical significance.

Results

Patient clinicopathologic characteristics are shown in Table 1. There were 781 men and 433 women. Their ages ranged from 22 to 89, with a median of 65 years. Clinicopathologic characteristics for pre-PLC and post-PLC are shown in Tables 2 and 3, respectively. For pre-PLC, definitive cytologic results were obtained in 1,194 patients, with a positive result in 38 (3.2%). Univariate analyses revealed significant differences between pre-PLC positive and negative patients in pathologic pleural involvement, pathologic N status, lymphatic permeation, vascular invasion, resection completeness, and scar grade. For post-PLC, definitive cytologic result was obtained in 1,182 patients, 54 (4.6%) of which showed a positive result. Significant differences were observed in pathologic stage, pathologic pleural involvement, pathologic N status, lymphatic permeation, vascular invasion, resection completeness, and scar grade between post-PLC positive and negative patients. The 5-year survival rate was 27% for positive pre-PLC patients, which was significantly worse than 71% for negative pre-PLC patients (Fig 1). The 10% 5-year survival rate for positive post-PLC patients was significantly worse 73% for negative post-PLC patients (Fig. 2).

Five-year survival rates for patients with negative pre-PLC and post-PLC (n = 1,094), positive pre-PLC and negative post-PLC (n = 21), negative pre-PLC and positive post-PLC (n = 37), and positive pre-PLC and positive post-PLC (n = 13) were 81, 50, 12, and 0%, respectively. Multivariate analyses revealed 6 independent prognostic factors when only factors available before lung resection were analyzed (Table 4): age, CEA level, cT factor, cN factor, sP factor, and pre-PLC result. When factors available after postoperative pathologic evaluation were included in multivariate analyses, however, 10 independent prognostic factors were recognized, but pre-PLC result was not (Table 5): Age, CEA level, cT factor, pT factor, pN factor, p factor, lymphatic invasion, vascular invasion, resection completeness, and post-PLC result.

Comment

The first report on PLC was in 1958 by Spjut and associates [10]. They reported the results of post-PLC in 49 patients with lung cancer undergoing surgical resection. The cytologic results were positive for malignant cells in 16 (33%) of them, but outcomes were not analyzed. In 1984, Eagan and colleagues [11] reported positive post-PLC in 12 (8.9%) of 135 patients. Lung cancer recurred in nine of the 12 patients, with only two in the

Table 4. Multivariate Analysis Results for Prognostic Factors Available Before Lung Resection

Variable	Hazard Ratio (95% CI)	*p* Value
Age	1.020 (1.006–1.035)	0.005
Gender	0.958 (0.638–1.436)	0.833
Smoking (S.I > 400)	0.963 (0.648–1.433)	0.853
CEA	1.732 (1.320–2.272)	<0.001
cT factor (2–4 vs 1)	0.624 (0.475–0.814)	0.002
cN factor (1–3 vs 0)	0.512 (0.379–0.691)	<0.001
sP factor (2–3 vs 1–2)	0.621 (0.475–0.814)	<0.001
Pre-PLC	2.980 (1.683–5.277)	<0.001

CEA = serum carcinoembryonic antigen; CI = confidence interval; PLC = pleural lavage cytology; S.I = smoking index.