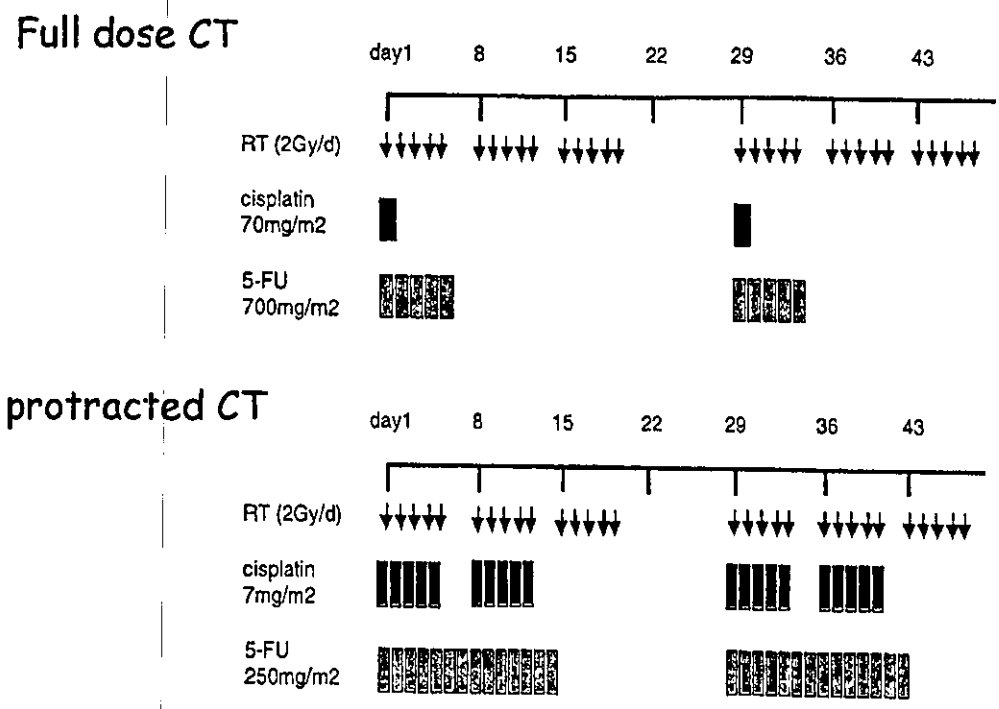

Fig. 5. Schematic of a randomized clinical trial of 5-fluorouracil (*5-FU*)/cisplatin concurrent chemoradiotherapy (CRT) for locally advanced esophageal cancer (Kyoto Radiation Oncology Study Group [KROSG-0101]; Japanese Radiation Oncology Study Group [JROSG-021]). In this randomized trial, protracted low-dose infusion CT (cisplatin, 7 mg/m^2 for 10 days; 5-FU, 250 mg/m^2 per 24 h for 14 days) was compared with short-term full-dose CT (cisplatin, 70 mg/m^2 for 1 day; 5-FU, 700 mg/m^2 for 5 days) combined with RT of 60 Gy over 7 weeks, with a 1-week split

68% of the dose to the auditory apparatus (mean dose, 36.7 vs 54.2 Gy) compared with conventional RT. By diminishing the dose to the auditory apparatus, the incidence of ototoxicity related to cisplatin was significantly reduced in patients treated by IMRT, although they received a higher dose of cisplatin than patients treated by conventional RT.

Improvement in drug delivery systems and the use of new chemotherapeutic drugs, including molecular targeting agents, are strategies for CRT. Conjugating drugs with polymeric carriers is one way of improving selective delivery to tumors. Poly (L-glutamic acid)-paclitaxel (PG-TXL) is one such conjugate.[34] Compared with paclitaxel, its uptake, tumor retention, and antitumor efficacy are increased. In an animal experiment, PG-TXL showed dramatically potentiated tumor radiocurability without affecting acute normal tissue injury. [34] Intraarterial infusion can also be used to deliver a higher concentration of CT to target tissues. Promising clinical results for combination intraarterial CT and RT have been reported for various tumors.[35] Unfortunately, no randomized clinical trial comparing intraarterial CT with intravenous CT combined with RT has been conducted.

In terms of molecular targeting, members of the erbB receptor tyrosine kinase family, particularly EGFR, are strong biomarkers of poor prognosis in head and neck cancer treated with RT.[19,20] Thus, new treatment strategies that counteract EGFR-mediated signaling are being exploited. Preclinical studies showed that treatment of human tumor xenografts with C225, a human-mouse chimeric anti-EGFR monoclonal antibody, markedly enhanced the tumor response to RT, as assessed by the tumor growth delay and the tumor cure rate.[20] The value of EGFR antagonists in a combined modality setting, particularly with RT, is being addressed in clinical trials.

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REVIEW ARTICLE

Yuichiro Ohe

Chemoradiotherapy for lung cancer: current status and perspectives

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Abstract For many years, thoracic radiotherapy had been regarded as the standard treatment for patients with unresectable locally advanced non-small cell lung cancer. However, meta-analyses show that cisplatin-containing chemoradiotherapy is significantly superior to radiotherapy alone in terms of survival. Moreover, concurrent chemoradiotherapy yields a significantly increased response rate and enhanced survival duration when compared with the sequential approach. Cisplatin-based chemotherapy with concurrent thoracic radiotherapy yields a 5-year survival rate of approximately 15% for patients with unresectable locally advanced non-small cell lung cancer. The state-of-the-art treatment for limited-stage small cell lung cancer is considered to be four cycles of combination chemotherapy with cisplatin plus etoposide combined with early concurrent twice-daily thoracic irradiation (45 Gy). If patients achieve complete remission, prophylactic cranial irradiation should be administered. A 5-year survival rate of approximately 25% is expected with the state-of-the-art treatment for limited-stage small cell lung cancer. Chemoradiotherapy is considered to be a standard treatment for both unresectable locally advanced non-small cell lung cancer and limited-stage small cell lung cancer. Several new strategies are currently being investigated to improve the survival of these patients. The incorporation of target-based drugs such as gefitinib is considered to be the most promising strategy for unresectable locally advanced non-small cell lung cancer. The incorporation of irinotecan is also a promising strategy to improve the survival of patients with limited-stage small cell lung cancer. The Japan Clinical Oncology Group is conducting clinical trials to develop new treatment strategies for both unresectable locally advanced non-small cell lung cancer and limited-stage small cell lung cancer.

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Introduction

Lung cancer is one of the most common carcinomas not only in Japan but also in the United States and Europe. Approximately 15%–20% of lung cancer patients have small cell lung cancer (SCLC) and the other patients have non-small cell lung cancer (NSCLC), such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. In Japan, more than 55 000 patients died of lung cancer in 2001, and mortality continues to rise.[1,2] In particular, the number of elderly lung cancer patients in Japan is increasing.[2] Lung cancer is the leading cause of cancer death in males in Japan and is anticipated to become the leading cause of cancer death in females.[1] However, the cure rate for lung cancer is still very low.

Surgery is the most effective curative treatment for early-stage NSCLC; however, only 30% of patients with NSCLC receive a curative resection.[3] Platinum-based chemotherapy offers a survival benefit and symptom relief for patients with metastatic NSCLC, and the combination of cisplatin-containing chemotherapy with thoracic radiotherapy has been considered as the standard treatment for patients with unresectable locally advanced NSCLC.[4] Approximately 15% of patients with unresectable locally advanced NSCLC can be cured by concurrent chemoradiotherapy.[5] Most patients with SCLC are not considered to be candidates for surgery. SCLC is one of the most chemosensitive solid tumors, and the outcome of SCLC patients is slowly but surely improving. Combination chemotherapy achieves a high response rate and survival prolongation for extensive-stage (ED) SCLC.[6–8] Combination chemotherapy consisting of cisplatin plus etoposide and concurrent twice-daily thoracic radiotherapy has yielded a 5-year survival rate of approximately 25% in limited-stage (LD) SCLC patients.[9,10] Chemoradiotherapy plays a very

important role in the treatment of both patients with unresectable locally advanced NSCLC and patients with LD-SCLC.

Chemoradiotherapy for non-small cell lung cancer

Patient selection

Most patients with stage I or II NSCLC are candidates for primary surgery with or without adjuvant chemotherapy. However, patients with superior sulcus tumor are candidates for induction chemoradiotherapy or radiotherapy followed by surgery.[11] Patients with stage IIIA and stage IIIB disease without pleural effusion, pericardiac effusion, and pleural dissemination are candidates for chemoradiotherapy. Only selected patients with stage IIIA NSCLC are considered to be candidates for surgery.[12] Chemoradiotherapy for unresectable locally advanced NSCLC achieves a long-term survival rate comparable to that of resectable N2 NSCLC after surgery.[5,13-15] Patients who are to receive chemoradiotherapy should have a good performance status and adequate organ function. If a patient is to receive radiotherapy with a radiation field including the contralateral hilum and more than half of the lung, such a patient should be excluded from concurrent chemoradiotherapy. Preexistent pulmonary fibrosis identified on plain chest X-ray film is reported to be a very strong risk factor for treatment-related death in thoracic radiotherapy, due to pneumonitis.[16,17] Thus, patients with pulmonary fibrosis identified on plain chest X-ray film should be excluded from chemoradiotherapy.

Chemoradiotherapy versus radiotherapy alone or chemotherapy alone

For many years, thoracic radiotherapy had been regarded as the standard treatment for patients with unresectable locally advanced NSCLC.[18,19] However, a meta-analysis of 1780 cases in 11 randomized trials showed that cisplatin-containing chemoradiotherapy was significantly superior to radiotherapy alone in terms of survival.[4] Other meta-analyses have also demonstrated the survival superiority of chemoradiotherapy compared with radiotherapy alone for patients with unresectable locally advanced NSCLC.[20,21] On the other hand, Kubota et al.[22] reported that the addition of radiotherapy to chemotherapy for locally advanced NSCLC significantly improved the 2- and 3-year survival rates compared to chemotherapy alone. Sculier et al.[23] reported the results of a randomized phase III trial that compared further chemotherapy and chest irradiation as a consolidation treatment after the achievement of a response to induction chemotherapy in patients with non-metastatic unresectable NSCLC. There was no significant difference in survival or response duration, but chest irradiation was associated with a significantly greater duration of local control than chemotherapy. Thus, the combination of cisplatin-containing chemotherapy with thoracic radiotherapy has been considered as the standard treatment for patients with unresectable locally advanced NSCLC.

Timing of chemotherapy and radiotherapy

Randomized phase III trials to compare the sequence schedule of chemoradiotherapy with concurrent chemoradiotherapy have been conducted by the Japan Clinical Oncology Group (JCOG)[14] and by the Radiation Therapy Oncology Group (RTOG[15]; Table 1). In the JCOG trial, 320 patients with unresectable locally advanced NSCLC were randomized to chemotherapy with cisplatin, vindesine, and mitomycin followed by radiotherapy (sequential arm) or concurrent chemoradiotherapy (concurrent arm). The response rate for the concurrent arm was significantly higher (84.0%) than that of the sequential arm (66%; $P = 0.0002$). The median survival time was significantly longer in patients receiving concurrent therapy (16.6 months), as compared with those receiving sequential therapy (13.3 months; $P = 0.03998$). The 2-, 3-, 4-, and 5-year survival rates in the concurrent group (34.6%, 22.3%, 16.9%, and 15.8%, respectively) were better than those in the sequential group (27.4%, 14.7%, 10.1%, and 8.9%, respectively). The concurrent approach yielded a significantly increased response rate and enhanced median survival time when compared with the sequential approach.[14] Similar results were reported from the RTOG trial.[15] The survival was significantly superior in the concurrent arm (with a median survival time of 17.0 months and a 4-year survival rate of 21%) than in the sequential arm (14.6 months and 12%, respectively; $P = 0.046$). This report also demonstrated the long-term survival benefit of the concurrent delivery of cisplatin-based chemotherapy with thoracic radiotherapy as compared with the sequential delivery of these therapies.[15] In these trials, acute toxicities, such as myelosuppression and esophagitis, were greater among patients on the concurrent arm than on the sequential arm. Based on these phase III trials, concurrent chemoradiotherapy appears to result in better survival than sequential therapy.

There are some limitations to the generalization of the results of these trials, because old-generation cisplatin-based combination chemotherapies were used in these trials: cisplatin and vindesine plus mitomycin, or cisplatin plus vinblastine.[14,15] These old-generation cisplatin-based chemotherapies could be combined with concurrent radiotherapy using a full dose. Several new anticancer agents were developed in the 1990s, such as irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine.[24-31] The combination of platinum and these new agents is more effective than the old-generation combination chemotherapy for metastatic NSCLC.[30,31] However, these new agents could not be combined with concurrent radiotherapy at the full dose.[32-35] A French cooperative group conducted a phase III trial to compare sequential versus concurrent chemoradiotherapy for unresectable NSCLC.[36] The sequential arm consisted of three cycles of cisplatin plus vinorelbine followed by thoracic radiotherapy. The concurrent arm consisted of two cycles of cisplatin plus etoposide with concurrent thoracic

Table 1. Randomized trials of sequential versus concurrent chemoradiotherapy

Author	Treatment	*n*	MST	2-Year Survival	5-Year Survival	*P* Value
Furuse[14]	CDDP + VDS + MMC; sequential TRT	158	13.3 Months	27.4%	8.9%	
	CDDP + VDS + MMC; concurrent TRT	156	16.6 Months	34.6%	15.8%	$P = 0.03998$
Curran[15]	CDDP + VBL; sequential TRT		14.6 Months	32%	12% (4-Year)	–
	CDDP + VBL; concurrent TRT	610 (Total)	17.0 Months	35%	21% (4-Year)	$P = 0.046$
	CDDP + ETOP; concurrent TRT (twice daily)		15.2 Months	34%	17% (4-Year)	$P = 0.296$
Pierre[36]	CDDP + VNR; sequential TRT	103	13.8 Months	23%		
	CDDP + ETOP; concurrent TRT f/b CDDP + VNR	104	15.0 Months	35%		$P = 0.41$
Zatloukal[37]	CDDP + VNR; sequential TRT	102 (Total)	396 Days			
	CDDP + VNR; concurrent TRT		619 Days			$P = 0.0216$

CDDP, cisplatin; VDS, vindesine; MMC, mitomycin; VBL, vinblastine; ETOP, etoposide; VNR, vinorelbine; TRT, thoracic radiotherapy; f/b, followed by

radiotherapy followed by two cycles of cisplatin plus vinorelbine. More than 200 patients were enrolled in this trial. The median survival time was 13.8 months in the sequential arm and 15.0 months in the concurrent arm. The 2-year survival rates were 23% and 35%, respectively.[36] While there was a trend in favor of concurrent therapy, it was not statistically significant ($P = 0.41$). There are no data from large phase III trials comparing sequential chemoradiotherapy using full-dose new-generation chemotherapy with concurrent chemoradiotherapy using reduced-dose new-generation chemotherapy. Only a small randomized phase II study has been reported[37] (Table 1).

Fractionation

Radical radiotherapy for NSCLC is most commonly given in daily fractions, Monday to Friday, for a total dose of 60–70 Gy over 6–8 weeks.[38,39] Novel fractionation schedules have been explored with the aim of improving local tumor control and survival without increasing late morbidity (Table 2).[40–51] In hyperfractionated radiotherapy, the dose per fraction is reduced and the total dose is increased to give improved tumor control without increased late morbidity. The RTOG clinical trials used hyperfractionated radiotherapy, 1.2 Gy/fraction, twice a day, for a total dose of 69.6 Gy.[40–42] However, this hyperfractionation schedule has not been shown to have significant benefit when compared to conventional radiotherapy plus chemotherapy.[15,41,42] Schild et al.[43] reported the results of a phase III study which compared split-course accelerated hyperfractionated radiotherapy (AHFRT), 1.5 Gy/fraction, twice a day (60 Gy) with standard radiotherapy (STDRT), 2 Gy/fraction, once a day (60 Gy) combined with concurrent chemotherapy. The toxicity, tumor control, and survival rates were similar with AHFRT and STDRT. The JCOG retrospectively compared STDRT and AHFRT from the data of six JCOG clinical trials.[5] In this study also, AHFRT did not show a clear tendency to improve the survival of the patients with locally advanced NSCLC. Twice-daily fractionation, both 1.2 Gy/fraction and 1.5 Gy/fraction twice a day, have not demonstrated any superiority compared with standard once-daily fractionation for patients with locally advanced NSCLC.[5,15,41–43]

More recently, continuous hyperfractionated accelerated radiotherapy (CHART) and hyperfractionated accelerated radiation therapy (HART) have been investigated.[45–51] CHART consisted of 36 small fractions of 1.5 Gy given three times per day, to give 54 Gy in only 12 consecutive days, including the weekend. CHART, compared with conventional radiotherapy, gave a significant improvement in the survival of patients with NSCLC.[45,46] However, this result was obtained from randomized phase III trials of radiotherapy alone. No randomized trials of chemoradiotherapy using CHART have been reported. HART consisted of a total dose of 57.6 Gy in 36 fractions, delivered over 15 days, with the use of three daily fractions with a 4-h interval between fractions and an 8-h interval between on-cord fields.[48,49] Patients are not treated on weekends. The results of a phase III study which compared standard thoracic radiotherapy with HART after induction chemotherapy for patients with unresectable NSCLC were reported from the Eastern Cooperative Oncology Group (ECOG).[50] The study was closed prematurely due to poor accrual. However, induction chemotherapy of carboplatin plus paclitaxel followed by HART resulted in an acceptable

Table 2. Once-daily versus multiple-daily radiotherapy for unresectable NSCLC

Author	Chemotherapy	Radiotherapy	*n*	MST (Months)	2-Year Survival	5-Year Survival	*P* Value
Sause[41,42]	Non	2 Gy/Day, 60 Gy, 5 days/week; continuous	163	11.4	21%	5%	–
	CDDP + VBL × 2; induction	2 Gy/Day, 60 Gy, 5 days/week; continuous	164	13.2	32%	8%	$P = 0.04$
	Non	1.2 Gy × 2/Day, 69.6 Gy, 5 days/week; continuous (HFRT)	163	12.0	24%	6%	NR
Schild[43]	CDDP + ETOP × 2; concurrent	2 Gy/Day, 60 Gy 5 days/week; continuous	117	14	37%	13%	
	CDDP + ETOP × 2; concurrent	1.5 Gy × 2/Day, 60 Gy, 5 days/week; split (AHFRT)	117	15	40%	20%	$P = 0.4$
Saunders[45,46]	Non	2 Gy/Day, 60 Gy, 5 days/week; continuous	225	NR	20%	NR	
	Nor	1.5 Gy × 3/Day, 54 Gy, 7 days/week; continuous (CHART)	338	NR	29%	NR	$P = 0.004$
Belani[50]	CBDCA + PTX × 2; induction	2 Gy/Day, 64 Gy, 5 days/week; continuous	56	13.7	30%	NR	
	CBDCA + PTX × 2; induction	1.5-1.8-1.5 Gy/Day, 57.6 Gy, 5 days/week; continuous (HART)	55	20.3	44%	NR	$P = 0.20$

NR, not reported; CDDP, cisplatin; VBL, vinblastine; ETOP, etoposide; CBDCA, carboplatin; PTX, paclitaxel; HFRT, hyperfractionated radiotherapy; AHFRT, accelerated hyperfractionated radiotherapy; CHART, continuous hyperfractionated accelerated radiotherapy; HART, hyperfractionated accelerated radiation therapy

toxicity profile and provocative efficacy, with a median survival of 20.3 months, in contrast to a median survival of 13.7 months in the standard thoracic radiotherapy arm.[50] Ishikura et al.[51] reported the results of a pilot study of HART following induction cisplatin and vinorelbine for stage III NSCLC. Thirty patients were enrolled in this study. The overall objective response rate was 83% and the median survival time was not reached. The 1- and 2-year overall survivals were 68% and 58%, respectively.[51] Further investigations of CHART or HART with chemotherapy are warranted.

Selection of anticancer agents

In the 1980s to the early 1990s, old-generation cisplatin-based chemotherapies, such as cisplatin plus etoposide, cisplatin plus vindesine, cisplatin plus vinblastine or cisplatin, and vindesine plus mitomycin, were commonly used in chemoradiotherapy with both sequential and a concurrent schedules for locally advanced NSCLC.[14,15] In the 1990s, several new anticancer agents were developed, such as irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine.[24–31] These new agents have different mechanisms of action from those of the old-generation agents. A full dose of the old-generation combination chemotherapy could be combined with concurrent radiotherapy.[14,15] However, if we wish to use the new-generation chemotherapy with thoracic radiotherapy, we have to use reduced-dose chemotherapy with concurrent thoracic radiotherapy, or full-dose chemotherapy followed by sequential radiotherapy.[32–34] No results of comparisons between the full-dose old-generation combination chemotherapy together with concurrent radiotherapy and the reduced-dose new-generation chemotherapy together with concurrent thoracic radiotherapy have been reported. Only very few reports have compared chemotherapy regimens used with concurrent thoracic radiotherapy. To evaluate the new drugs, gemcitabine, paclitaxel, and vinorelbine, in combination with cisplatin in unresectable locally advanced NSCLC, the Cancer and Leukemia Group B (CALGB) conducted a randomized phase II study of two cycles of induction chemotherapy followed by two additional cycles of the same drugs with concomitant radiotherapy.[33] One hundred and seventy-five patients received four cycles of cisplatin at 80 mg/m^2 on days 1, 22, 43, and 64, with gemcitabine 1250 mg/m^2 on days 1, 8, 22, and 29 and 600 mg/m^2 on days 43, 50, 64, and 71; or paclitaxel 225 mg/m^2 for 3 h on days 1 and 22 and 135 mg/m^2 on days 43 and 64; or vinorelbine 25 mg/m^2 on days 1, 8, 15, 22, and 29 and 15 mg/m^2 on days 43, 50, 64, and 71. Radiotherapy was initiated on day 43, at 2 Gy/day, for a total dose of 66 Gy. Response rates after the completion of radiotherapy were 74%, 67%, and 73% for the gemcitabine, paclitaxel, and vinorelbine arms, respectively. The median survival times were 18.3 months (95% confidence interval [CI], 13.8 to 23.6), 14.8 months (95% CI, 12 to 19.5), and 17.7 months (95% CI, 12.4 to 24.7) for the gemcitabine, paclitaxel, and vinorelbine arms, respectively.[33] No consistent standard chemotherapy regimens for chemoradiotherapy have been established.

Concomitant low-dose daily or weekly chemotherapies also use radiotherapy as a radiosensitizer. Cisplatin or

carboplatin are commonly used in studies to investigate sensitizing effects.[52-55] Of the numerous single-platinum studies, only one phase III study demonstrated the survival benefit of daily administration of cisplatin with thoracic radiotherapy. Two studies demonstrated prolonged survival with concomitant platinum-based multidrug chemotherapy and hyperfractionated radiotherapy.[56,57] No data from large phase III studies have been reported to compare full-dose chemotherapy with low-dose sensitizing chemotherapy combined with concurrent radiotherapy for locally advanced NSCLC. CALGB conducted a phase III study to compare low-dose weekly carboplatin plus paclitaxel with concomitant radiotherapy (arm 1) and induction chemotherapy with carboplatin plus paclitaxel followed by the same concomitant chemoradiotherapy (arm 2) for stage III NSCLC.[58] Three hundred and sixty-six patients were entered in this study. The median survival on arm 1 was 11.4 months, versus 14.0 months on arm 2, and the 1-year survival rates were 48% and 54%, respectively ($P = 0.154$). The median survival achieved in each of the treatment groups was low compared to results in other recent trials. This result indicated that low-dose weekly carboplatin plus paclitaxel with concomitant radiotherapy might be insufficient treatment for stage III NSCLC.

The Southwest Oncology Group (SWOG) conducted a phase II study of concurrent chemoradiotherapy with cisplatin plus etoposide followed by consolidation docetaxel in stage IIIB NSCLC.[59] Treatment consisted of cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 on days 1 through 5 and 29 through 33; and concurrent thoracic radiotherapy, for a total dose of 61 Gy. Consolidation docetaxel was started 4 to 6 weeks after chemoradiotherapy, at an initial dose of 75 mg/m^2. Eighty-three eligible patients were entered in this study. The median survival was 26 months, and the 1-, 2-, and 3-year survival rates were 76%, 54%, and 37%, respectively.[59] These results were much better than the results of the previous SWOG trial. Phase III trials evaluating docetaxel consolidation have been initiated to validate these results.

Future directions

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, such as gefitinib (ZD1839) and erlotinib (OSI-774), are some one of the most promising target-based agents for NSCLC.[60-62] EGFR tyrosine kinase inhibitors have shown encouraging antitumor activity for NSCLC in phase II studies. Moreover, it has been reported that gefitinib potentiated the efficacy of radiotherapy in human colorectal cancer and human squamous cell carcinoma in head and neck xenograft models.[63-67] Thus, the combination of gefitinib with chemoradiotherapy is a candidate strategy to improve the survival of patients with unresectable locally advanced NSCLC. The JCOG has started a safety and efficacy trial of cisplatin and vinorelbine followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced NSCLC (JCOG 0402-MF).

Chemoradiotherapy for small cell lung cancer

Patient selection

SCLC is generally classified into two stages, LD and ED.[68,69] In the consensus reports of the International Association of Lung Cancer (IASLC), LD is defined as disease involvement of one hemithorax, including ipsilateral pleural effusion and regional lymph nodes, including the ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular nodes.[68] Patients with LD-SCLC, except for those with ipsilateral malignant pleural effusion and ipsilateral pulmonary metastasis, are considered to be candidates for chemoradiotherapy. Patients requiring radiotherapy with a radiation field of more than half of the lung, or those with preexistent pulmonary fibrosis identified on plain chest X-ray film, should be excluded from chemoradiotherapy.[16,17]

Standard chemoradiotherapy for small cell lung cancer

A meta-analysis including 13 trials and 2140 patients with LD-SCLC demonstrated the survival benefit of chemoradiotherapy as compared with chemotherapy alone.[70] The relative risk of death in the chemoradiotherapy group as compared with the chemotherapy group was 0.86 (95% CI, 0.78 to 0.94; $P = 0.001$), corresponding to a 14% reduction in the mortality rate. The benefit in terms of overall survival at 3 years was 5.4%. Based on this meta-analysis, chemoradiotherapy is considered to be the standard treatment for LD-SCLC. In this meta-analysis, non-platinum-based combination chemotherapies were commonly used, and only a few trials used platinum-based modern chemotherapy. Cisplatin plus etoposide is now widely regarded as the standard chemotherapy for LD-SCLC, particularly because this regimen can be integrated with concurrent thoracic irradiation, with acceptable toxicity.[71] Early thoracic irradiation with concurrent cisplatin-plus-etoposide chemotherapy is the state-of-the-art treatment for LD-SCLC.

A United States intergroup trial demonstrated the survival benefit of twice-daily accelerated thoracic radiotherapy over once-daily radiotherapy with cisplatin plus etoposide for LD-SCLC[10] (Table 3). Four hundred and seventeen LD-SCLC patients were randomized to receive a total of 45 Gy of concurrent thoracic radiotherapy, given either twice daily over a 3-week period or once daily over a period of 5 weeks. The median survival was 19 months for the once-daily group and 23 months for the twice-daily group. The 2-year and 5-year survival rates for patients receiving once-daily radiotherapy were 41% and 16%, and these rates for the twice-daily group were 47% and 26% ($P = 0.04$ by log-rank test).[10] In contrast, another phase III trial, using split-course twice-daily radiotherapy, failed to demonstrate a survival benefit of twice-daily over once-daily radiotherapy with cisplatin plus etoposide.[72,73] A split schedule of radiotherapy seemed to diminish the benefit of twice-daily radiotherapy (Table 3).

The brain is one of the most common sites of relapse of SCLC. However, the central nervous system is protected

Table 3. Twice-daily versus once-daily radiotherapy for LD-SCLC

Author	Chemotherapy	Radiotherapy	*n*	MST (Months)	5-Year Survival	*P* Value
Turrisi[10]	CDDP + ETOP × 4	1.5 Gy × 2/Day, 45 Gy, 1st cycle, continuous	211	23	26%	
	CDDP + ETOP × 4	1.8 Gy/Day, 45 Gy, 1st–2nd cycles, continuous	206	19	16%	$P = 0.04$
Bonner[72] Schild[73]	CDDP + ETOP × 6	1.5 Gy × 2/Day, 48 Gy, 4th–5th cycles, split	130	20.6	22%	
	CDDP + ETOP × 6	1.8 Gy/Day, 50.4 Gy, 4th–5th cycles, continuous	132	20.6	21%	$P = 0.68$

CDDP, cisplatin; ETOP, etoposide

from anticancer drugs by the blood-brain barrier. Several phase III trials have demonstrated that prophylactic cranial irradiation (PCI) reduces the incidence of brain metastasis in patients with SCLC, but no phase III trials have demonstrated a survival benefit of PCI for patients with SCLC.[74–76] A meta-analysis, using individual data on 987 patients with SCLC in complete remission (CR) who took part in seven trials that compared PCI with no PCI demonstrated a survival benefit of PCI.[77] The relative risk of death in the PCI group as compared with the no-PCI group was 0.84 (95% CI, 0.73 to 0.97; $P = 0.01$), which corresponds to a 5.4% increase in the rate of survival at 3 years (15.3% in the no-PCI group vs 20.7 % in the PCI group). This absolute improvement in 3-year survival (5.4%) was the same as that shown in a meta-analysis comparing chemotherapy with chemoradiotherapy for SCLC.[70,77] Thus, PCI for SCLC, in patients who have achieved a complete response (CR), has a power to improve survival similar to that of thoracic radiotherapy for LD-SCLC.

The state-of-the-art treatment for LD-SCLC is considered to be four cycles of combination chemotherapy with cisplatin plus etoposide, combined with early concurrent twice-daily thoracic irradiation (45 Gy). If patients achieve a CR, PCI should be administered. A 5-year survival rate of approximately 25% is expected with the state-of-the-art treatment for LD-SCLC.

Future directions

The JCOG conducted a randomized multicenter phase III study of irinotecan plus cisplatin versus etoposide plus cisplatin for previously untreated patients with ED-SCLC (JCOG 9511).[8] One hundred and fifty-four patients were randomized, 77 into each arm. The median survival time was 12.8 months in the irinotecan-plus-cisplatin arm and 9.4 months in the etoposide-plus-cisplatin arm. The irinotecan-plus-cisplatin arm showed significantly better survival compared with standard treatment with etoposide plus cisplatin ($P = 0.002$; unadjusted one-sided log-rank test). Treatment with four cycles of irinotecan plus cisplatin every 4 weeks in ED-SCLC patients yielded a highly significant improvement in survival, with less myelosuppression, over the standard etoposide plus cisplatin.[8] Thus, the incorporation of

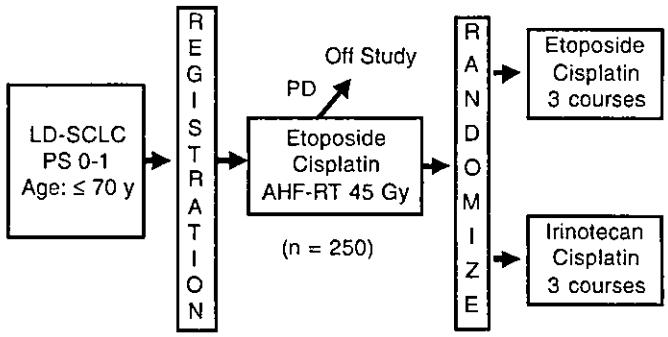

Fig. 1. Ongoing randomized phase III trial in patients with limited-stage small cell lung cancer (LD-SCLC) by Japan Clinical Oncology Group (JCOG; JCOG 0202MF). *PS*, performance status; *PD*, progressive disease; *AHF-RT*, accelerated hyperfractionated radiotherapy

irinotecan into the treatment for LD-SCLC is considered to be one of the most important strategies for improving the survival of LD-SCLC patients. Concurrent twice-daily thoracic radiotherapy with combination chemotherapy consisting of irinotecan and cisplatin may be the most powerful treatment for LD-SCLC patients if it is possible to use the full dose of irinotecan with acceptable toxicity. Previously, the JCOG conducted a dose-finding study of irinotecan and cisplatin plus concurrent radiotherapy for unresectable stage III NSCLC (JCOG 9405).[32] The dose intensity of irinotecan in the study was low, because of the need to omit irinotecan administration on days 8 and/or 15 as a result of leukopenia or diarrhea, and the radiotherapy completion rate was also low. This was a very small study, however, and chemotherapy with full-dose irinotecan and cisplatin plus concurrent radiotherapy was deemed unacceptable based on the results of the JCOG 9405 study. Full-dose chemotherapy consisting of etoposide and cisplatin can be used in combination with concurrent radiotherapy. However, when irinotecan is used as a single agent with concurrent radiotherapy, the dose of irinotecan must be reduced from 100 mg/m^2 to 60 mg/m^2 in a weekly schedule.[78] This dose reduction of irinotecan likely reduces the efficacy of irinotecan in the treatment of LD-SCLC patients. The JCOG is conducting a phase III study (JCOG 0202-MF) of concurrent twice-daily thoracic radiotherapy with four

cycles of etoposide and cisplatin as the standard arm versus, concurrent twice-daily thoracic radiotherapy with etoposide and cisplatin, followed by three cycles of chemotherapy with the standard dose of irinotecan and cisplatin (Fig. 1).

Conclusion

Chemoradiotherapy is considered to be the standard treatment for both unresectable locally advanced NSCLC and LD-SCLC. Cisplatin-based chemotherapy with concurrent thoracic radiotherapy yields a 5-year survival rate of approximately 15% for patients with unresectable locally advanced NSCLC. Cisplatin plus etoposide with concurrent twice-daily thoracic radiotherapy yields a 5-year survival rate of approximately 25% for patients with LD-SCLC. Several new strategies are currently underway to investigate improvements in survival for these patients. The incorporation of target-based drugs, such as gefitinib, is considered to be the most promising strategy for unresectable locally advanced NSCLC. The incorporation of irinotecan is also a promising strategy to improve the survival of patients with LD-SCLC. The JCOG is presently conducting clinical trials to develop a new strategy for the treatment of both unresectable locally advanced NSCLC and LD-SCLC.

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Original article

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A phase II study of cisplatin and docetaxel administered as three consecutive weekly infusions for advanced non-small-cell lung cancer in elderly patients

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Background: To evaluate the efficacy and safety of treatments for advanced non-small-cell lung cancer in elderly patients aged 75 years or older, we conducted a phase II study of cisplatin and docetaxel administered in three consecutive weekly infusions.

Patients and methods: The eligibility criteria for the study included the presence of chemotherapy-naive advanced non-small-cell lung cancer, age ≥75 years, Eastern Cooperative Oncology Group performance status of 0 or 1, a measurable lesion, adequate organ functions and signed informed consent. The chemotherapy regimen consisted of cisplatin (25 mg/m^2) and docetaxel (20 mg/m^2) on days 1, 8 and 15 every 4 weeks.

Results: Between February 2000 and March 2002, 34 elderly patients with non-small-cell lung cancer were enrolled in the study and 33 patients were treated. Two complete responses and 15 partial responses were obtained for an objective response rate of 52% in 33 treated patients. The median survival period was 15.8 months, and the 1-year survival rate was 64%. Toxicities were mild with no grade 4 toxicities. Only grade 3 leukopenia (6%), neutropenia (12%), anemia (3%), hyponatremia (3%) and nausea/vomiting (3%) were observed.

Conclusion: Cisplatin and docetaxel administered in three consecutive weekly infusions was safe and effective for the treatment of elderly patients with chemotherapy-naive non-small-cell lung cancer.

Key words: cisplatin, docetaxel, elderly patients, non-small-cell lung cancer, weekly administration

Introduction

Lung cancer is one of the most common carcinomas not only in Japan, but also in the United States and Europe. More than 55 000 patients die from lung cancer each year, and the mortality rate is still increasing in Japan [1, 2]. In particular, the number of elderly lung cancer patients is increasing in Japan [1, 2]. Surgery is the most effective curative treatment for early stage non-small-cell lung cancer (NSCLC); however, only 30% of patients with NSCLC receive a curative resection [3]. Cisplatin-based chemotherapy offers a survival benefit and symptom relief for patients with inoperable NSCLC [4]. However, we have demonstrated that classic standard cisplatin-based chemotherapy regimens such as cisplatin (80 mg/m^2) on day 1 with etoposide (100 mg/m^2) on days 1–3 or cisplatin (80 mg/m^2) on day 1 with vindesine (3 mg/m^2) on days 1 and 8 cause severe myelotoxicity in elderly NSCLC patients aged ≥75 years [5]. We used a very restricted eligibility criteria to select patients who could tolerate the cisplatin-based standard chemotherapy. Among 34 elderly patients, only 10 fitted the eligibility criteria. In spite of granulocyte colony-stimulating factor (G-CSF) support, nine of the 10 eligible patients experienced grade 4 neutropenia and six had infectious episodes [5]. Thus, we hypothesized that the recommended dose for elderly patients aged ≥75 years should be determined in a specific phase I study only for elderly patients.

Docetaxel has demonstrated antitumor activity in NSCLC patients with chemotherapy-naive lesions and tumor progression after receiving cisplatin-based regimens [6–10]. Docetaxel with cisplatin is one of the most promising chemotherapy regimens for NSCLC [11]. The commonly used dose and schedule of docetaxel is 60–100 mg/m^2 every 3 weeks; however, moderate to severe neutropenia is frequently observed [6–11]. Recent studies have shown that weekly administration of docetaxel produces a higher dose intensity and less myelotoxicity [12–14]. Thus, we conducted two independent phase I studies for elderly and non-elderly patients with NSCLC to determine the recommended dose for phase II studies and to evaluate the safety and efficacy of cisplatin and docetaxel administered as three consecutive weekly infusions in both non-elderly (≤74 years) and elderly (≥75 years) patients

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[15]. Different recommended doses of docetaxel were obtained for non-elderly and elderly patients [15]. The recommended doses were 25 mg/m^2 cisplatin and 35 mg/m^2 docetaxel on days 1, 8 and 15 for non-elderly patients, and 25 mg/m^2 cisplatin and 20 mg/m^2 docetaxel on days 1, 8 and 15 for elderly patients.

Two phase II studies of cisplatin and docetaxel administered as three consecutive weekly infusions for non-elderly and elderly patients were conducted. The results of the phase II study for non-elderly patients with NSCLC have been reported elsewhere; the objective tumor response was 30% [95% confidence interval (CI) 15% to 46%] and the median survival time was 12.8 months [16]. Here, we report the promising results of a phase II study for elderly patients with NSCLC.

Patients and methods

Patient selection

Patients with histologically and/or cytologically documented NSCLC were eligible for the study. Each patient was required to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy), an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, age ≥75 years, no prior chemotherapy, measurable lesions, adequate hematological function [white blood cell count (WBC) 4000–12 000/mm^3; neutrophils ≥2000/mm^3; platelets ≥100 000/mm^3; hemaglobin ≥9.0 g/dl], adequate hepatic function (total bilirubin <1.1 mg/dl, aspartate aminotransferase and alanine aminotransferase <60 IU/l), and adequate renal function (creatinine ≤1.2 mg/dl, creatinine clearance ≥60 ml/min). Patients with active infection, severe heart disease, uncontrollable hypertension or diabetes mellitus, active concomitant malignancy and pleural and/or pericardial effusion requiring drainage were excluded. The study was approved by the Institutional Review Board at the National Cancer Center, Yokohama Municipal Citizen's Hospital and Niigata Cancer Center. Written informed consent was obtained from each patient.

Patient evaluation

The pretreatment evaluation consisted of complete blood cell count, differential count, routine chemistry measurements, a chest radiograph, a chest computed tomography (CT) scan, abdominal ultrasound or CT scan, whole-brain magnetic resonance imaging or CT scan, and an isotope bone scan. Complete blood cell count, differential, count and routine chemistry measurements were carried out at least twice a week during the first course of chemotherapy.

Treatment schedule

All patients were admitted to hospital during the first course of chemotherapy. Chemotherapy consisted of cisplatin (25 mg/m^2) on days 1, 8 and 15 and docetaxel (20 mg/m^2) on days 1, 8 and 15 every 4 weeks. Docetaxel was infused over 30 min with 16 mg dexamethasone and 3 mg granisetron administered just before the docetaxel infusion. Ninety minutes after the completion of the docetaxel infusion, 25 mg/m^2 cisplatin were administered over 15 min with 1500 ml normal saline over 3.5 h. The prophylactic administration of G-CSF was not permitted. Administration of G-CSF was permitted in patients with grade 4 neutropenia and/or leukopenia or grade 3 febrile neutropenia. The administration of both cisplatin and docetaxel were skipped on day 8 and/or day 15 if the patients met the following criteria: WBC <2000/mm^3 and/or platelets <50 000/mm^3. No dose modifications were carried out on days 8 and/or day 15 of the cisplatin and docetaxel administrations. Treatment was carried out for at least two courses, unless unacceptable toxicity or disease progression occurred.

Response and toxicity evaluation

The patients' responses were evaluated according to the World Health Organization criteria [17]. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) was defined as a reduction of ≥50% in the product of the largest perpendicular diameters of one or more clearly measurable lesions or as a >50% reduction in evaluable malignant disease lasting for >4 weeks with no new areas of malignant disease. No change included: the regression of indicator lesions that were insufficient to meet the criteria for PR, <25% increase in any measurable lesion and no new lesions of malignant disease. Progressive disease was defined as an increase in any measurable lesion by >25% or a new lesion of malignant disease. Survival times from the start of treatment were calculated using the Kaplan–Meier method. The toxicity grading criteria of the Japan Clinical Oncology Group (JCOG) were used to evaluate toxicity [18]. Most detailed gradings for individual organ toxicity in the JCOG Toxicity Criteria are identical to those of the National Cancer Institute Common Toxicity Criteria proposed in 1988. The only differences in the definitions used in the present study were that neutrophils were used instead of granulocytes and the definitions for nausea and vomiting were combined.

Statistical analysis

According to the minimax two-stage phase II study design by Simon [19], the treatment program was designed to refuse response rates of 20% and to provide a significance level of 0.05 with a statistical power of 80% in assessing the activity of the regimen as a 40% response rate. The upper limit for first-stage drug rejection was four responses among 18 evaluable patients; the upper limit of second-stage rejection was 10 responses among 33 evaluable patients. Overall survival was defined as the interval between enrolment in this study and death or the last follow-up visit. Median overall survival was estimated using the Kaplan–Meier analysis method [20].

Results

Patient characteristics

Between February 2000 and March 2002, 34 elderly patients with NSCLC were enrolled and 33 were treated in this study (Table 1). One patient did not receive the protocol treatment because the PS of the patient decreased before the start of the treatment and the patient no longer met the eligibility criteria. All treated patients were assessed for response, survival and toxicity. The median age of the patients was 77 years (range 75–86). The gender, PS and histology of the patients were as follows: 26 males, seven females; seven patients with PS 0, 26 patients with PS 1; 20 patients with adenocarcinoma, nine patients with squamous cell carcinoma, three patients with large cell carcinoma and one patient with NSCLC. Twenty-four patients had no prior treatment, five patients had undergone surgery, three patients had received radiotherapy for brain and/or bone metastases, and one patient had undergone both surgery and radiotherapy as prior treatments.

Treatment received and dose intensity

The total number of treatment cycles was 101 and the median was 3 (range 1–15). Two patients received only one course because of a decrease in their PS. Of the 33 treated patients, 12 patients received two courses, 13 received three and six received four or more. One patient received 15 courses; however, he received

Table 1. Characteristics of treated patients

No. of entered patients	34
No. of treated patients	33
Sex	
Male	26
Female	7
Age (years)	
Median	77
Range	75–86
PS (ECOG)	
0	7
1	26
Histology	
Adenocarcinoma	20
Squamous-cell carcinoma	9
Large-cell carcinoma	3
Non-small-cell	1
Stage	
IIIA	1
IIIB	9
IIIB with effusion	3
IV	17
Relapse	6
Prior treatment	
None	24
Radiotherapy	4
Surgery	6

PS (ECOG): performance status (Eastern Cooperative Oncology Group).

treatments on only days 1 and 15 of the fifth to fifteenth courses. Between the first and fourth cycles, 77–100% of the patients received treatments on days 8 and 15 treatment (Table 2). Of the 303 planned administrations, 272 (90%) were carried out.

The median actual dose intensities of docetaxel and cisplatin were 13.4 mg/m^2 (range 8.9–16.4) and 16.7 mg/m^2 (range 11.1–20.4) per week, whereas the projected dose intensities were 15.0 and 18.8 mg/m^2 per week for docetaxel and cisplatin, respectively.

Objective tumor response and overall survival

The objective tumor response is shown in Table 3. Two CRs and 15 PRs occurred for an objective response rate of 52% (95% CI 31% to 67%) in 33 treated patients. The overall survival periods of all treated patients are shown in Figure 1. The median survival time of the 33 treated patients was 15.8 months with a median follow-up time for 11 censored patients of 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

Table 2. Treatment received

No. of treatment cycles	No. of patients	Treatment received on	
		Day 8	Day 15
1	33	31 (94%)	32 (97%)
2	31	28 (90%)	24 (77%)
3	19	19 (100%)	17 (89%)
4	6	5 (83%)	5 (83%)
5	2	1 (50%)	1 (50%)

Toxicity

The worst grades of hematological and non-hematological toxicities experienced by each patient are listed in Table 4. Both hematological and non-hematological toxicities were relatively mild. No grade 4 hematological or non-hematological toxicities were observed. Only grade 3 leukopenia (6%), neutropenia (12%), anemia (3%), hyponatremia (3%) and nausea/vomiting (3%) were observed. None of the patients received G-CSF. Renal toxicity was also relatively mild: grade 2 renal toxicity was observed in only one of 33 patients.

Discussion

We previously reported that classic standard cisplatin-based chemotherapy regimens cause severe myelotoxicity in elderly patients aged ≥75 years [5]. Based on that previous study of elderly patients with NSCLC, we conducted phase I studies in which cisplatin and docetaxel were administered as three consecutive weekly infusions in both non-elderly and elderly patients with NSCLC using the same eligibility criteria, except for age, and the same definitions of dose-limiting toxicity and maximum-tolerated dose [15]. Our hypothesis was that the recommended dose for elderly patients aged ≥75 years would differ from that for non-elderly patients. In the previous phase I studies, we demonstrated a difference in the recommended dose of docetaxel combined with cisplatin between non-elderly and elderly patients [15]. The recommended doses of docetaxel with 25 mg/m^2 cisplatin were 35 and 20 mg/m^2 on days 1, 8 and 15 for non-elderly and elderly patients, respectively. We also conducted phase II studies for non-elderly and elderly patients with NSCLC using each recommended dose and the same eligibility criteria, except for age. The

Table 3. Response rate

No. of patients	CR	PR	NC	PD	NE	Response rate (95% CI)
33	2	15	13	2	1	52% (31% to 67%)

CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response.

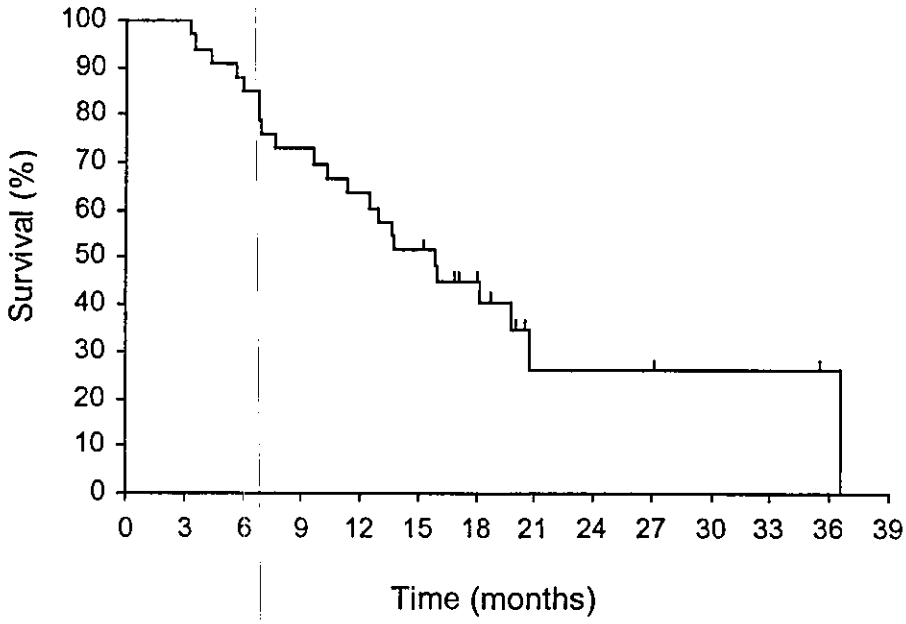

Figure 1. Overall survival time. The median survival time of the 33 treated patients was 15.8 months, and the median follow-up time for 11 censored patients was 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

Table 4. Maximum toxicity grades associated with weekly docetaxel and cisplatin in 33 treated patients

	Grade (Japan Clinical Oncology Group)					Grade ≥3
	0	1	2	3	4	
Leukopenia	13	6	12	2	0	6%
Neutropenia	16	5	8	4	0	12%
Anemia	9	8	15	1	–	3%
Thrombocytopenia	30	2	1	0	0	0
Nausea/vomiting	12	10	10	1	–	3%
Hyponatremia	22	8	2	1	0	3%
Diarrhea	23	6	4	0	0	0
Infection	32	1	0	0	0	0
Fever	27	4	2	0	0	0
Bilirubin	25	–	8	0	0	0
Transaminase	25	8	0	0	0	0
Creatinine	28	4	1	0	0	0
Fatigue	26	6	1	0	0	0

results of the phase II study for non-elderly patients with NSCLC have been reported elsewhere [16]. Among the 33 evaluable patients, an objective tumor response of 30% (95% CI 15% to 46%) and a median survival time of 12.8 months were observed [16]. In the current study, we observed an objective tumor response of 52% (95% CI 31% to 67%) and a median survival time of 15.8 months for elderly patients with NSCLC. In spite of the lower dose of docetaxel, the efficacy of the treatment did not seem to be diminished.

Italian oncology groups have conducted randomized trials for elderly patients aged ≥70 years [21–23]. In these studies, non-platinum-based single or double chemotherapy regimens, such as vinorelbine alone or vinorelbine plus gemcitabine were used for elderly patients with NSCLC [21–23]. These chemotherapy regimens might not be adequate for non-elderly patients with a good PS because the cisplatin plus vinorelbine regimen was significantly superior to vinorelbine alone with regard to both the response rate and the survival [24, 25]. Kubota et al. [26] reported that the frequency of grade 4 leukocytopenia in the elderly (≥70 years of age) group was significantly greater than in the non-elderly group and that no difference in overall survival was observed between the two groups. Langer et al. [27] reported that advanced age alone

Table 5. Chemotherapy for elderly patients with non-small-cell lung cancer

Study	Chemotherapy	Age (years)	No. of patients	PS 2 (%)	Stage III (%)	RR (%)	MST
ELVIS [21]	None	≥70	78	24	28	–	21 weeks
	VNR 30 mg/m^2 days 1, 8 q3 weeks		76	24	26	20	28 weeks
	VNR 30 mg/m^2 days 1, 8 q3 weeks		233	19	29	18	36 weeks
MILES [22]	GEM 1200 mg/m^2 days 1, 8 q3 weeks	≥70	233	18	30	16	28 weeks
	GEM 1000 mg/m^2 + VNR 25 mg/m^2 days 1, 8 q3 weeks		232	19	31	21	30 weeks
SICOG [23]	VNR 30 mg/m^2 days 1, 8 q3 weeks	≥70	60	22	42	15	18 weeks
	GEM 1200 mg/m^2 + VNR 30 mg/m^2 days 1, 8 q3 weeks		60	27	40	22	29 weeks
MPCRN [29]	DTX 36 mg/m^2 weekly × 6 q8 weeks	≥65[a]	39	41	31	18	5 months
Current study	CDDP 25 mg/m^2 + DTX 20 mg/m^2 days 1, 8, 15 q4 weeks	≥75	33	0	29	52	15.8 months (69 weeks)

[a]Or poor candidates for combination chemotherapy due to coexistent medical illness.

ELVIS, The Elderly Lung Cancer Vinorelbine Italian Study; MILES, Multicenter Italian Lung Cancer in the Elderly Study; SICOG; Southern Italy Cooperative Oncology Group; MPCRN, Minnie Pearl Cancer Research Network.

CDDP, cisplatin; DTX, docetaxel; GEM, gemcitabine; VNR, vinorelbine.

MST, median survival time; PS, performance status; RR, response rate.

should not preclude appropriate NSCLC treatment, although elderly patients aged ≥70 years have more co-morbidities and can expect a higher incidence of leukopenia and neuropsychiatric toxicity. In the United States, upper age limits are not included in eligibility criteria to avoid age discrimination. In contrast, most Japanese studies have upper age limits because Japanese government guidelines recommend that elderly patients, >75 years, should not be accrued in common clinical trials [28]. This recommendation was made in concern for the safety of elderly patients. In Japan, most clinical trials include patients aged ≤74 years, and the full-dose chemotherapy is administered. Clinical trials for elderly patients have generally been conducted as specific trials focusing on the treatment of elderly patients in Japan. However, the definition of 'elderly' is still unclear. Thus, the use of platinum-based chemotherapy in elderly patients with NSCLC remains controversial because no randomized phase III studies have been conducted to resolve this question.

Several chemotherapy trials for elderly patients with NSCLC have been reported [21–23, 29] (Table 5). Of the subjects in these trials, 18–41% were PS 2 patients. Eligible patients were 70 or 65 years or older. The response rates of the non-platinum-based single or double chemotherapy regimens ranged from 15% to 22%, and the median survival times ranged from 18 to 36 weeks [21–23, 29]. In the current study, however, PS 2 patients were excluded and only patients aged ≥75 years were included. The objective response rate of 52% (95% CI 31% to 67%) and the median survival time of 15.8 months (69 weeks) in our trial were extremely better than those of previous trials. We considered that the main reason for the better results was the exclusion of PS 2 patients. However, cisplatin chemotherapy might be important not only for non-elderly, but also for elderly patients with NSCLC.

We divided the cisplatin and docetaxel dosages on days 1, 8 and 15 because full-dose cisplatin is too toxic for elderly patients. The weekly administration of docetaxel produces a higher dose intensity and less myelotoxicity [12–14]. Moreover, a weekly schedule may be safer than a 3-weekly schedule because treatment on day 8 and/or day 15 can be omitted if severe toxicity is observed. In the current study, the toxicity, including nausea/vomiting and renal toxicity, was relatively mild, and 90% of the planned administrations were carried out. The dose-limiting toxicities of docetaxel administered in six consecutive weekly infusions were reported to be fatigue and asthenia [12–14]. In the previous phase I study, two out of six patients refused chemotherapy on day 15 because of fatigue and asthenia at level 2: 25 mg/m^2 cisplatin and 25 mg/m^2 docetaxel [15]. However, fatigue and asthenia were relatively mild in the current study because of the relatively low-dose of docetaxel (20 mg/m^2).

We conclude that cisplatin and docetaxel administered as three consecutive weekly infusions is very effective and safe for elderly patients with chemotherapy-naive NSCLC. The JCOG is conducting a phase III study of cisplatin and docetaxel versus docetaxel alone, administered as three consecutive weekly infusions, for elderly patients with NSCLC to examine the role of cisplatin in the treatment of elderly patients with NSCLC.

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Genomic-wide cDNA microarray screening to correlate gene expression profile with chemoresistance in patients with advanced lung cancer

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We conducted a study using cDNA microarray analysis to determine whether expression levels of genes in tumors were correlated with tumor response to chemotherapy. Between September 2000 and December 2001, 47 patients were registered in the study. Eighteen patients had small cell lung cancer (SCLC), and others had non-small cell lung cancer (NSCLC). All patients except three received platinum-based chemotherapy. Sixteen of the 18 patients with SCLC (89%) and 13 of the 29 patients with NSCLC (45%) responded to chemotherapy, respectively. Transbroncheal biopsy specimens of tumors were obtained before chemotherapy. The expression levels of 1176 genes in tumor specimens were analyzed using the Atlas™ Human Cancer 1.2 Array. When we analyzed the data for correlations between gene expression levels and tumor response to chemotherapy, there was a significant increase in the expression of nine genes in non-responders compared with responders to chemotherapy ($p< 0.01$). Multivariate regression analysis revealed that allogenic inflammatory factor, HLA-DR antigen associated invariant subunit and MHC class II HLA-DR-beta precursor were independent chemo-resistant factors ($p<0.0001$). When we analyzed the differences in gene expression levels between patients with SCLC and NSCLC, expression levels of one or more resistant genes were increased in comparison with the mean expression of control house keeping genes in five of 18 SCLC patients and 19 of 29 NSCLC patients, respectively ($p=0.012$).

In conclusion, some chemo-resistant genes were detected in the tumor tissue of lung cancer patients using cDNA microarray analysis. A prospective study is required to confirm whether expression levels of these genes reflect chemosensitivity.

Key words: microarray, chemoresistance, gene, lung, cancer

INTRODUCTIONN

Lung cancer is a leading cause of cancer death and most patients with this disease are candidates for chemotherapy. Small cell lung cancer (SCLC) is one of the most chemosensitive tumors, and reduces by chemotherapy in 80 to 90% of the patients. On the other hand, non-small cell lung cancer (NSCLC) is moderately effective responsive to chemotherapy and reduces by chemotherapy in 30 to 40% of the patients. The mechanisms of the difference of in chemosensitivity between SCLC and NSCLC patients have not been sufficiently enough examined, although responders to chemotherapy may have a better prognosis than non-responders (1). On the contrary, a large proportion of cancer patients suffer adverse

effects of with chemotherapy while showing no effective response in terms of tumor regression. Accordingly, it is important to be able to predict likely responders before subjecting patients to chemotherapy. Unfortunately, no reliable predictor of response has not yet been found.

A linear correlation was reported between the extent of gene-specific damage in human adenocarcinoma cells in pleural effusions and in mononuclear cells of peripheral blood (MNC) from lung cancer patients exposed to cisplatin *in vitro* prior to chemotherapy (2). When we examined the extent of gene-specific damage in MNC incubated with cisplatin *in vitro* before chemotherapy, the DNA damage to MNC was greater in responders in to chemotherapy showed that DNA damage in MNC was greater than that in non-responders (3). The PCR-stop assay measures DNA damage in specific genes and can be applied used to the measurement of DNA damage caused by a variety of anticancer agents. We have also demonstrated that this assay can detect the difference in DNA damage between VP-16-sensitive and resistant cells (4), and that it may be able to detect differences in other topoisomerase- related anticancer drugs such as CPT-11 (4). But use of this assay requires that cells should be treated with anticancer drugs before analysis. Moreover, the assay detects only DNA damage in treated cells and could does not clarify which genes influence to a patient's response in to chemotherapy.

The properties of cancer cells are determined by complicated interactions among all gene products expressed in cancer cells, and it is certain that many proteins – including enzymes involved in apoptosis, in DNA repair, and in the metabolism and detoxification of drugs – have individual responses.

The cDNA microarray method is now widely used to analyze the expression of thousands of genes simultaneously in cancer tissues, and its development has facilitated the analysis of genome-wide expression profiles that can generate a large body of information concerning genetic networks related to the response of tumors response to various drugs and the identification ofto identify genes involved in pathological conditions. Thus, the cDNA microarray analysis is a promising method for identifying genes associated with the sensitivity of tumors to various anticancer drugs, using amplified RNA extracted from a very small piece of biopsy sample from cancer patients. (5,6)

Large-scale gene expression microarray studies of lung cancer (7,8) have shown that altered expression of various genes is associated with a significantly worse prognosis. Theose data were under the influenced by of several factors, such as the response of the tumor effect ofto chemotherapy, the adverse effects of chemotherapy on patients, by chemotherapy and tumor progression and metastasis. The genetic informations are is required with regard to not only survival but also tumor response to effect and adverse effects by with chemotherapy.

Staunton *et al.* identified putative predictive markers of chemosensitivity and showed the feasibility of chemosensitivity prediction by transcriptional profiling (7). Different sets of genes were identified which may act as predictive markers for chemosensitivity to drugs in human cancer cell lines or tumor tissues using cDNA microarray (8-10). However, in these studies the predictive markers were identified as using *in vitro* or animal experiments, although the markers are required to be able to predict chemosensitivity in human cancer chemotherapy.

Therefore, we used cDNA microarray screening in the following study to examine the expression levels of specific genes expressions in tumor tissue, which was obtained through by transbroncheal biopsy, in order to determine any correlations withe tumor effect response to chemotherapy using cDNA microarray.

PATIENTS AND METHODS

Patients

This study was approved by the Institutional Review Boards of Kanagawa Cancer Center. The patients with histologically proven lung cancer treated with chemotherapy were entered into the present study. All were eligible for treatment. They had an expected survival of at least 6 six weeks,; measurable lesions,; Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≤ 3; white blood count $\geq$ 4,000/μl; hemoglobin $\geq$ 10 g/dl; platelet count $\geq$ 100,000/μl,; total serum bilirubin < 2 mg/d; aspartate aminotransferase and alanine aminotransferase less than twice the upper limit of the normal range; serum creatinine $\leq$ 1.5 mg/dl; and creatinine clearance > 50 ml/min. None of the patients had received prior chemotherapy for the primary lesion. Written informed consent for chemotherapy and a genetic analysis of tumor tissue was obtained in every case.

Chemotherapy

All patients with non-progressive cancer were treated with two or more courses of chemotherapy. Response criteria were evaluated according to the World Health Organization (WHO) criteria (11).

Tumor samples

Transbroncheal biopsy specimens of tumors were obtained before chemotherapy. The half of the

specimens were fixed in formalin-fixed for use for pathological diagnosis and another the other half were immediately frozen for storage at -80°c until genetic analysis.

Extraction and Purification of RNA and Preparation of Probes

The total RNA of each sample was isolated and treated with DNase I to avoid contamination of genomic DNA by silica membrane affinity chromatography using Macherey-Nagel's total RNA isolation kit (MACHEREY-NAGEL GmbH & Co. KG, Germany). One hundred nanograms of the total RNA for each sample was reverse transcribed into cDNA and amplified by SMART polymerase chain reaction (PCR) technology (Chenchik et al.12) with using the Super SMART™ PCR cDNA Synthesis kit (BD Biosciences Clontech, CA, USA) according to the manufacturer's instructions. To represent the expression profile of the starting initial total RNA material, the optimal conditions for PCR cycling determined for each sample by testing the amplified cDNA with gel electrophoresis. All samples were amplified for 19 to 23 cycles. Each cDNA sample was subjected to microarray expression profioling with using the BD Atlas™ Human Cancer 1.2 Array (Clontech) based on the manufacturer's protocol. The following is a brief overview of the procedures used is as follows. A Rradioactively labeled probe mixture for hybridization with array membranes was synthesized from each cDNA sample by using the CDS Primer Mix specific for the Atlas™ Human Cancer 1.2 Array and [α-^{32}P] dATP.

cDNA Microarray

Each of the labeled probe was then hybridized into a separate Atlas Array. After appropriate washing, array membranes were exposed to a phosphor screen and the signal intensity for each spot, which corresponds to each gene examined, was determined by using a STORM image analyzer (Amersham Bioscience, Picataway, NJ). The hybridization pattern and signal intensity were analyzed to determine changes in gene expression levels using AtlasImage™ 2.01 software (CLONTECH, Laboratory, Inc., Japan).

Statistical methods

T-tests were used to identify differences in mean expression levels between responders and non-responders to chemotherapy. Fisher's exact and χ^2 tests were used to assess whether the frequency of gene - expression was associated with an objective response to chemotherapy. $P < 0.001$ was considered to be significant.

Table I. *Patient characteristics*

				No. of patients
Total				47
Gender	Male			36
	Female			11
Smokers				38
PS(ECOG)	0			5
	1			30
	2			9
	3			3
Pathology	SCLC	Stage	LD	2
			ED	16
	NSCLC	Stage	IIB/IIIA	4
			IIIB	8
			IV	17

PS, performance status; ECOG, Eastern Cooperative Oncology Group;

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer;

LD, limited disease; ED, extensive disease.

RESULTS

Between September 2000 and December 2001, 47 patients were registered in the study. Patient characteristics are summarized in Table I. Thirty-six patients were male and eleven were female, with a median age of 66 years (range 35–81 years). Thirty-eight patients were smokers. The PS was 0 for five patients; 1 for 30 patients; 2 for nine; and 3 for three patients. Eighteen patients had SCLC, and the remaining had NSCLC. Of the patients with SCLC, 2 two had limited disease and the other 16 had extensive SCLC. Of the patients with NSCLC, four had stage IIB/IIIA, eight had stage IIIB, and 17 had stage IV. No patients had receivedno prior chemotherapy.

All patients except three who had been sub-scribedreceived paclitaxel and irinotecan received were given platinum-based chemotherapy. Three of patients with SCLC and seven of patients with NSCLC received thoracic radiotherapy concurrently or sequentially with chemotherapy (Table II). 16 of the 18 patients with SCLC (89%) and 13 of the 29 patients with NSCLC (45%) responded to chemotherapy, respectively.

The expression levels of 1176 genes expression in the tumor specimens were analyzed using cDNA microarray screening. Four housekeeping genes which were expressed in every all 47 tumor samples in the present study were used as controls for gene