S-1 Plus Cisplatin with Concurrent Radiotherapy for Locally Advanced Non-small Cell Lung Cancer

A Multi-Institutional Phase II Trial (West Japan Thoracic Oncology Group 3706)

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Purpose: To evaluate the combination chemotherapy using oral antimetabolite S-1 plus cisplatin (SP) with concurrent thoracic radiotherapy (RT) followed by the consolidation SP for locally advanced non-small cell lung cancer.

Patients and Methods: Patients with stage III non-small cell lung cancer, 20 to 74 years of age, and Eastern Cooperative Oncology Group performance status 0 to 1 were eligible. The concurrent phase consisted of full dose S-1 (orally at 40 mg/m^2/dose twice daily, on days 1–14) and cisplatin (60 mg/m^2 on day 1) repeated every 4 weeks for two cycles with RT delivered beginning on day 1 (60 Gy/30 fractions over 6 weeks). After SP-RT, patients received an additional two cycles of SP as the consolidation phase.

Results: Fifty-five patients were registered between November 2006 and December 2007. Of the 50 patients for efficacy analysis, the median age was 64 years; male/female 40/10; Eastern Cooperative Oncology Group performance status 0/1, 21/29; clinical stage IIIA/IIIB 18/32; and adenocarcinoma/others 20/30. There were 42 clinical responses including one complete response with an objective response rate of 84% (95% confidence interval [CI], 71–93%). The 1- and 2-year overall survival rates were 88% (95% CI, 75–94%) and 70% (95% CI, 55–81%), respectively. The median progression-free survival was 20 months. Of the 54 patients for safety analysis, common toxicities in the concurrent phase included grade 3/4 neutropenia (26%), thrombocytopenia (9%), and grade 3 esophagitis (9%) and febrile neutropenia (9%). In one patient, grade 3 pneumonitis was observed in the consolidation phase. There were two treatment-related deaths caused by infection in the concurrent phase.

Conclusions: SP-RT showed a promising efficacy against locally advanced NCSLC with acceptable toxicity.

Key Words: Concurrent chemoradiotherapy, Non-small cell lung cancer, Phase II trial, S-1, Cisplatin.

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The standard treatment modality in patients with unresectable stage III non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy.[1] Nevertheless, this combined treatment is associated with greater acute toxicity, including bone marrow[2] suppression, pneumonitis, and esophagitis,[2] compared with the sequential combination of chemotherapy and radiotherapy (RT). About a decade ago, we developed a concurrent chemoradiotherapy regimen using uracil-tegafur (UFT, Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) plus cisplatin (UP) with concurrent thoracic RT (2 Gy per fraction, total 60 Gy) (UP-RT).[3] The response rate and median survival time of locally advanced unresectable stage III (IIIA 20%, IIIB 80%) patients treated with the UP-RT were 80% and 16.5 months, respectively, and these figures are similar to those reported in other concurrent chemoradiotherapy trials.[4,5] Nevertheless, the incidence of leukopenia and esophagitis of grade 3 or 4 was 16% and 3% of the patients, respectively,[3] and these figures are far lower than those of other trials.

S-1 (TS-1, Taiho Pharmaceutical Co., Ltd) is a second-generation oral anticancer agent based on uracil-tegafur, which has a dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine. S-1 comprises tegafur (a 5-FU Pro-

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drug), 5-chloro-2, 4-dihydroxypyridine (an inhibitor of DPD), and potassium oxonate (an inhibitor of phosphoribosyl transferase), in a molar ratio of 1:0.4:1 and has been shown to induce a comparable response to the other single agents for metastatic NSCLC.[6] Furthermore, combination chemotherapy using S-1 plus cisplatin (SP) for advanced NSCLC has been reported to show a response rate of 33 to 47% and a median survival time of 11 to 16 months.[7,8] Those data were better than the usual response rate of 29 to 38% and the median survival time of 8 to 13 months for the combination chemotherapeutic regimens using UP,[9,10] whereas the frequency of severe hematological and nonhematological adverse events induced by both UP and SP was lower than that of other platinum-based combination regimens such as carboplatin plus paclitaxel (CP), cisplatin plus docetaxel, and so on.[11–13] In addition, West Japan Oncology Group (WJOG) recently demonstrated that chemotherapy using S-1 plus carboplatin was noninferior in terms of overall survival (OS) compared with CP in advanced NSCLC.[14]

The above-mentioned observations indicated that it might be possible to use the same dose of SP as is used for metastatic advanced NSCLC for the treatment of locally advanced NSCLC with concurrent thoracic RT, similar to UP-RT. If this is possible, SP and concurrent thoracic RT (SP-RT) would be expected to provide several advantages over UP-RT. First, SP could have stronger antitumor activity for both locally advanced NSCLC and micrometastatic lesions than UP. Second, although both cisplatin and 5-FU have been reported to have a radiosensitizing effect,[15,16] the level of the latter in the blood by SP could not only be maintained at a higher level than by UP[17,18] but also 5-chloro-2, 4-dihydroxypyridine in S-1 has been recently reported to have a radiosensitizing effect as well as a strong DPD activity.[19,20] A single-institutional experience with SP-RT in 11 patients was reported showing that all the patients had a partial response, with acceptable hematological and nonhematological toxicities. On the basis of these findings, the WJOG (formally, West Japan Thoracic Oncology Group) conducted a multi-institutional phase II trial to confirm the antitumor effects and safety of SP-RT.

PATIENTS AND METHODS

Eligibility Criteria

The eligibility requirements for enrollment in this phase II trial were cytologically or histologically confirmed, unresectable stage III NSCLC, for which radical dose RT could be prescribed. The staging was performed according to the 6th edition of tumor, node, metastasis (TNM). All patients were required to meet the following criteria: measurable disease; an Eastern Cooperative Oncology Group performance status of 0 or 1; a projected life expectancy of more than 3 months; a leukocyte count of $\geq$4000/μL; a platelet count of $\geq$100,000/μL; a blood gas oxygen level of $\geq$70 torr; a serum bilirubin level below 1.5 mg/dL; serum glutamic oxaloacetic transaminase/glutamic pyruvic transaminase levels of no more than 100 IU/ml; a creatinine level of $\leq$1.2 mg/dL; and a creatinine clearance level of $\geq$60 mL/min. Other eligibility criteria included no prior treatment and an age $<$75 years. All eligible patients underwent computed tomography (CT) scans of the thorax and upper abdomen and a radioisotope bone scan. Patients who had malignant pleural effusion, malignant pericardial effusion, a concomitant malignancy, or serious concomitant diseases were excluded from the study. Written informed consent was required from all patients, and the protocol was approved by the institutional ethics committee of each participating institute. All data were centrally monitored by the WJOG datacenter. This study is registered with the University Hospital Medical Information Network in Japan (number 000001370).

Treatment Schedule

Chemotherapy with SP

S-1 (40 mg/m^2/dose) in the form of 20 and 25 mg capsules containing 20 and 25 mg of tegafur, respectively, were taken orally twice a day after meals between days 1 and 14 as follows: in a patient with a body surface area (BSA) $<$1.25 m^2, 40 mg twice daily; for those with BSA 1.25 m^2, but $<$1.5 m^2, 50 mg twice daily; and BSA $>$1.5 m^2, 60 mg twice daily. Cisplatin (60 mg/m^2) was administered as a $\geq$120-minute infusion on day 1. The patients were also hydrated with 1000 to 2000 mL saline by infusion before cisplatin was administered. An antiemetic agent was administered at the discretion of each patient's physician.

The combination chemotherapy with SP was repeated twice, with a 4-week interval, concurrently with thoracic RT (SP-RT). At 2 to 4 weeks after the completion of the concurrent chemoradiotherapy, two further cycles of the same SP regimen were administered as a consolidation chemotherapy as shown in Figure 1.

A leukocyte count of 3000/μL or greater and the entry eligibility criteria regarding organ functions had to be satisfied for the patients to start the next cycle. If these criteria were satisfied 4 weeks after day 1 of each cycle of chemotherapy, the next cycle was administered. The doses of S-1 were adjusted according to the degree of hematological and nonhematological toxicity. The dose was reduced by one level (20 mg day) in patients whose BSA was 1.25 m^2 or more if there was evidence of grade 4 hematologic toxicity or grade 3 or more nonhematological toxicity during any cycle

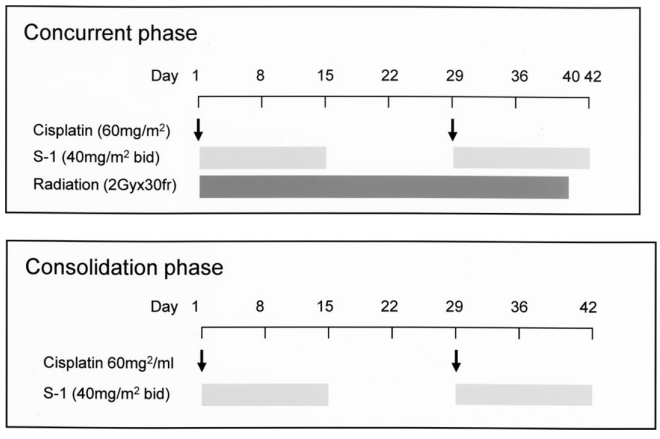

FIGURE 1. Treatment schedule.

of administration. If recovery from such toxicities was confirmed at a reduced dose, administration at the reduced dose was continued. If a patient with a BSA less than 1.25 m^2 experienced the above toxicities, then no further treatment with S-1 was performed. If a rest period of more than 4 weeks between two chemotherapy cycles of concurrent and consolidation phases was required or if the consolidation chemotherapy could not start within 6 weeks after SP-RT, then the SP treatment was discontinued.

Radiotherapy

All patients were treated with a linear accelerator photon beam of 6 MV or more from day 1. The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over a period of 6 weeks. In this protocol, both 2- and 3-dimensional (D) treatment planning systems were allowed. The radiation doses were specified at the center of the target volume. The doses were calculated assuming tissue homogeneity without correcting for lung tissues for both 2- and 3-D treatment planning. Among the 54 patients assessable for toxicity, 2- and 3-D treatment planning were performed for 7 and 47 patients, respectively. The initial 40 Gy/20 fractions were delivered to clinical target volume 1 (CTV1), and the final 20 Gy/10 fractions were delivered to a reduced volume defined as clinical target volume 2 (CTV2). CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal (no. 2) to subcarinal lymph nodes (no. 7). For the primary tumors and the involved lymph nodes of 1 cm or more larger in the shortest diameter, a margin of at least 0.5 cm was added. The contralateral hilum was not included in CTV1. The supraclavicular areas were not treated routinely but were treated when the supraclavicular nodes were involved. CTV2 included only the primary tumor and the involved lymph nodes, with a margin of 0.5 to 1 cm. The spinal cord was excluded from the fields for CTV2 by appropriate methods, such as the oblique opposing method. The appropriate planning target volume margin and leaf margin were added for CTV1 and CTV2. When grade 4 hematologic toxicity, grade 3 to 4 esophagitis or dermatitis, pyrexia of $\geq$38°C, or a decrease in the partial pressure of arterial oxygen of 10 torr or more were compared with that before RT occurred, RT was interrupted. If a rest period of more than 2 weeks was required, then the patient was withdrawn from the study.

Evaluation of the Response and Toxicity

All registered patients, excluding those withdrawn from the study, received the following evaluations. Chest x-rays, complete blood cells, and blood chemistry studies were repeated once a week during the treatment period. Thoracic CT was performed every 1 or 2 months during the treatment period. After the treatment, a thoracic CT was obtained every 6 months, and other imaging examinations were obtained when recurrence was suspected. The response was evaluated in accordance with the RECIST version 1.0 guidelines.[21] In this study, the results of the response which an investigator determined were not used, and all responses were confirmed by the board members of the independent response review.

During the evaluation of both the initial staging and the antitumor effects, an extramural review was conducted. Only patients whose initial clinical stage was judged to be stage IIIA and IIIB and who were eligible for the study were analyzed for the response to treatment. The toxicity for all patients who received any treatment was assessed and graded by using the National Cancer Institute Common Terminology Criteria for Adverse Event version 3.

Statistical Analysis

The primary end point of this study was the objective tumor response rate. On the basis of the assumption that a response rate of higher than 80% would be expected from the combined modality treatment, while a rate below 60% would make a further investigation unnecessary, a sample size of 49 patients was required by the exact binomial test with a one-sided alpha error of 0.05 and a beta error of 0.1. Therefore, a total of 55 patients was the planned accrual size in view of possibly including ineligible patients. For determining the response rate, the exact binomial confidence interval (CI) was calculated. OS was defined as the time from registration until death from any cause. Progression-free survival (PFS) was defined as the time between registration and disease progression or death. The Kaplan-Meier method was used to estimate OS and PFS curves. All statistical analyses were done with SAS version 9.1.

RESULTS

Characteristics of Patients

Between November 2006 and December 2007, a total of 55 patients were enrolled from 18 institutes. One patient withdrew his consent and four patients were found to be ineligible by the extramural review (one malignant effusion, one carcinomatous lymphangitis, and 2 stage IV diseases). Therefore, the efficacy analyses were performed for the 50 remaining eligible patients. Safety analyses were performed for 54 patients who underwent SP-RT. Table 1 shows that 80% of the 50 eligible patients were male, with a mean age of 63 years (range, 40–74 years). Squamous cell carcinoma was the most common histological diagnosis, including 48% of the patients, and most patients had clinical stage IIIB disease (IIIA versus IIIB; 36% versus 64%). The most frequently classified TNM categories were T1-3N2 (36%), T1-3N3M0 (28%), and T4N0-1M0 (18%).

Adverse Events

The major adverse events (grade 3 and 4 toxicities) of SP-RT are listed in Table 2. Among the hematologic toxicities of the concurrent phase, grade 3 or higher leukopenia and neutropenia was observed in 17 patients (32%) and 14 patients (26%), respectively. Five patients (9%) developed grade 3 or higher thrombocytopenia. Among the nonhematologic toxicities, grade 3 and 4 febrile neutropenia was observed in four (7%) and one (2%) patient, respectively, whereas grade 3 esophagitis occurred in 4 patients (7%). Although no cases of severe pneumonitis occurred in the concurrent phase, two patients had a treatment-related death: one patient died of sepsis soon after the completion of the

TABLE 1. Patient Characteristics

No. of eligible patients	50
Age, yrs	
Mean (range)	63 (40–74)
Gender	
Male	40 (80%)
Female	10 (20%)
ECOG PS	
0	21 (42%)
1	29 (48%)
Smoking history	
Absent	2 (4%)
Present	48 (96%)
Histology	
Squamous cell carcinoma	24 (48%)
Adenocarcinoma	20 (40%)
Others	6 (12%)
cTNM	
Stage IIIA	18 (36%)
T1-3N2	18 (36%)
Stage IIIB	32 (64%)
T1-3N3M0	14 (28%)
T4N0-1M0	9 (18%)
T4N2M0	7 (14%)
T4N3M0	2 (4%)
Location of primary site	
Upper lobe	36 (72%)
Middle lobe	4 (8%)
Lower lobe	8 (16%)
Others	2 (4%)

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

TABLE 2. Hematological and Nonhematological Major Adverse Events

	Concurrent Chemoradiotherapy (n = 54)			Consolidation Chemotherapy (n = 39)		
	Grade			Grade		
Toxicities	3	4	Frequency of 3 or 4 (%)	3	4	Frequency of 3 or 4 (%)
Hematological						
Leukopenia	12	5	31.5	6	0	15.4
Neutropenia	10	4	25.9	4	0	10.3
Thrombocytopenia	1	4	9.3	4	0	10.3
Anemia	4	2	11.1	7	1	20.5
Nonhematological						
Febrile neutropenia	4	1	9.3	0	0	
Nausea	1	1	3.7	0	0	
Vomiting	2	0	3.7	0	0	
Anorexia	6	1	13.0	0	0	
Creatinine	0	0		0	0	
AST/ALT	1	1	3.7	0	0	
Diarrhea	2	0	3.7	0	0	
Stomatitis	1	0	1.9	0	0	
Pneumonitis	0	0		1	0	2.6
Esophagitis	4	0	7.4	1	0	2.6

AST, aspartate transaminase; ALT, alanine aminotransferase.

TABLE 3. Radiation Delivered (N = 50)

Radiation dose (Gy)	
Median (range)	60.0 (28–60)
Average	58.4
Reasons for interruption, N (%)	
Adverse events	7 (14.0)
Other	2 (4.0)
Rate of completion of treatment with 60 Gy, N (%)	47 (94.0)

TABLE 4. Chemotherapy Delivered (N = 50)

	N (%)
Concurrent chemotherapy	
Chemotherapy cycles	
1	50 (100)
2	46 (92.0)
Reasons for discontinuation	
Adverse event	2 (4.0)
Patient decision	2 (4.0)
Reasons for not proceeding to consolidation chemotherapy	
Adverse event	8 (16.0)[a]
Other	1 (2.0)
Consolidation chemotherapy	
Chemotherapy cycles	
1	37 (74.0)
2	31 (62.0)
Reasons for discontinuation	
Adverse event	5 (10.0)
Disease progression	1 (4.0)
Rate of completion of 4 cycles of treatment (95% CI)	62% (47.2–75.3)

[a] Two treatment-related deaths were included after completion of concurrent chemotherapy.
CI, confidence interval.

concurrent phase and the other patient died of pneumonia after the recovery from the bone marrow suppression because of that phase.

Thirty-nine (72%) of the 54 patients proceeded to consolidation chemotherapy. As shown in Table 2, the frequency of grade 3 or 4 in any major toxicity caused by consolidation chemotherapy was lower than that in concurrent chemoradiotherapy, except for anemia and pneumonitis. It was of note that no febrile neutropenia was observed.

Treatments Delivered to Eligible Patients

Tables 3 and 4 show RT and chemotherapy delivered to 50 eligible patients, respectively. Forty-six patients (92%) completed two cycles of SP concurrent with thoracic RT of 60 Gy. Two patients refused further protocol treatment after one cycle of chemotherapy because of adverse events. The other two patients did not meet the criteria to start the second cycle of SP because of prolonged neutropenia. Although 46 patients completed the concurrent phase of the SP-RT, seven patients could not proceed to the consolidation phase because of mainly prolonged hematological toxicity, and two patients

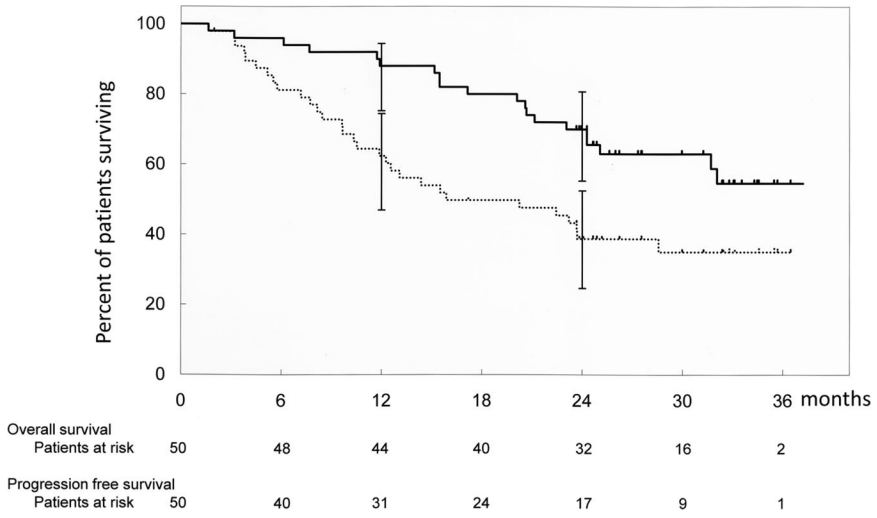

FIGURE 2. Overall survival (▬) and progression-free survival (▪▪▪▪▪▪). Each *tick* represents one patient who is alive with/without recurrence. The *bars* represent the 95% confidence intervals of the survival rate at 1 and 2 years after treatment.

were lost to treatment-related death. Of 37 patients, one and five patients received only one cycle of the consolidation chemotherapy because of disease progression and adverse events, respectively. Thus, a total of 31 (62%) of the 50 eligible patients received all four cycles of SP chemotherapy.

Response

Of the 50 patients eligible for efficacy analysis, 42 patients had responses (84%; 95% CI, 71–93%; $p < 0.0001$), including 1 patient with a complete response, and 2 patients with stable disease. Only one patient showed progressive disease. Five patients were unevaluable for a response. There were no differences in the response rate by histology (88% in squamous cell carcinoma versus 81% in others, $p = 0.704$ by the exact binomial test).

Survival

The overall median follow-up time for the 29 patients who were still alive as of January 2010 was 28 months (range, 24–37 months). As shown in Figure 2, the median PFS and OS was 20 months and not reached, respectively, and the OS rates at 1 and 2 years were 88% (95% CI, 75–94%) and 70% (95% CI, 55–81%), respectively.

Sites of First Failures

With respect to the sites of first failure among the 28 (56%) patients with disease progression of the 50 eligible patients, 19 (38%), 6 (21%), and 3 (6%) patients had distant metastases, intrathoracic local diseases, and both, respectively. Those nine occurred in the irradiated field. The frequently observed initial distant metastases were observed in bone in eight patients and in brain and lung in four each. Only four patients (8%) developed a brain metastasis alone as the initial failure site.

DISCUSSION

The purpose of concurrent chemoradiotherapy for NSCLC patients with stage III disease is to achieve local control, for which RT plays the main role, and also to eradicate occult distant metastases by chemotherapy. For the latter purpose, the development of regimens that can allow administration of the systemic (full) doses of chemotherapy during RT is necessary. Although the so-called "third generation" agents such as paclitaxel, vinorelbine, docetaxel, and gemcitabine have been evaluated in several concurrent studies in combination with platinum compounds, a lower dose of that agent plus the platinum compound has generally been used due to toxicities. Therefore, induction chemotherapy with sufficient systemic doses of the agents was considered a potentially effective addition to the concurrent chemoradiotherapy.[22] Nevertheless, a recent randomized trial (CALGB 39801) showed that two cycles of induction chemotherapy with full doses of CP did not provide a survival benefit over concurrent chemoradiotherapy alone, using weekly CP at lower doses.[23] Furthermore, the randomized phase III trial conducted by the Hoosier Oncology Group and U.S. Oncology Group demonstrated that the addition of consolidation chemotherapy using docetaxel after full-dose chemotherapy using cisplatin plus etoposide with concurrent RT (PE-RT) failed to achieve the primary end point of improved survival compared with PE-RT alone.[24] On the basis of these randomized trials, concurrent chemotherapy alone is recommended for the treatment of locally advanced-NSCLC. However, the optimal chemotherapy regimen remains to be determined.

In this study, SP-RT using systemic doses had the advantage of eradicating occult distant metastases. In addition, 5-FU has been reported to have a radiosensitizing effect in preclinical and clinical studies of various cancers, including NSCLC,[15,16] and S-1 is orally administered for 14 consecutive days in each course of chemotherapy, providing long-term potential radiosensitization. The antitumor effects of SP-RT might explain the high response rate of 82% and the prolonged median PFS of 20 months, as well as the median OS, which was not reached when follow-up time ranged from 24 to 37 months. Another SP-RT phase II trial with a similar schedule and dose, which was conducted during almost the same period as the present trial, also demonstrated a good overall response rate of 88%, median PFS of 12 months, and a median OS of 33 months, whereas the median follow-up

time was 25 months, ranging from 12 to 38 months.[25] Nevertheless, these data cannot be directly compared with our data. In this trial, the extraordinarily good results may not be only because of the chemotherapy regimen but also to the high frequency of the primary site being within the upper lobe. In completely resected NSCLC with N2 disease, the 5-year survival rate in patients with their primary site in the upper lobe is well known to be significantly better than that of patients with the primary tumor in the lower lobe.[26] In addition, the tumors in the upper lobe with upper mediastinal nodal metastases are easier to treat with RT than the tumors in the lower lobe in terms of the irradiation field.

Two additional cycles of the same chemotherapy after concurrent chemoradiotherapy were called consolidation chemotherapy in this trial. Although the original PE-RT regimen used two additional cycles of the same PE after PE (two cycles)-RT, the above-mentioned randomized trial did not use consolidation PE in both control and experimental groups.[24] Similarly, the original mitomycin, vindesine plus cisplatin (MVP)-RT regimen had the two additional cycles of the same MVP[5] after MVP (two cycles)-RT, whereas a recent randomized trial used MVP (two cycles)-RT alone as a control arm.[27] The median OS of PE (2 cycles)-RT and MVP (2 cycles)-RT was 23.2 and 23.7 months, respectively.[24,27] In addition, only 41% of the patients could complete four cycles of MVP in the MVP-RT group of a recent WJTOG phase III trial (WJTOG0105), which had a median OS of 20.5 months.[28] In this trial, 62% of the patients completed four cycles of SP despite a low frequency of severe toxicities, whereas the WJOG phase III trial showed that the safest regimen with concurrent RT was CP among MVP, CP, and carboplatin plus CPT-11, although the completion rate of two cycles in the consolidation chemotherapy of CP arm was only 50%.[28] These observations suggest that a phase III trial is necessary to clarify whether or not a total of four cycles of chemotherapy in this setting provides a better result than two cycles of chemoradiotherapy.

The irradiated dose of 60 Gy in 30 fractions with concurrent chemotherapy is currently used in the majority of institutes in Japan, whereas that of 66 Gy in 33 fractions in combination with chemotherapy in the United States seems to be the most common treatment regimen. Because PET/CT scan and 3-D planning were not used in all patients, it would therefore be interesting to elucidate whether or not the present survival of such patients can be prolonged by these techniques, including a total irradiated doses of 66 Gy.

Although the present treatment with SP-RT should be acceptably safe in terms of the frequency of grade 3 and 4 adverse events, the treatment-related death of two patients was observed. Therefore, it is necessary to keep in mind that there is no totally safe regimen for concurrent chemoradiotherapy. At present, the WJOG is conducting a randomized phase II trial comparing SP-RT to combination chemotherapy using cisplatin plus vinorelbine with concurrent RT.

REFERENCES

1. Pfister DG, Johnson DH, Azzoli CG, et al; American Society of Clinical Oncology. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–353.
2. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181–2190.
3. Ichinose Y, Nakai Y, Kudoh S, et al. Uracil/tegafur plus cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer: a multi-institutional phase II trial. *Clin Cancer Res* 2004;10:4369–4373.
4. Curran W, Scott C, Langer C. Phase III comparison of sequential vs concurrent chemoradiation for pts with unresected stage III non-small cell lung cancer (NSCLC): Initial report of Radiation Therapy Oncology Group (RTOG) 9410. *Lung Cancer* 2000;29(93s, suppl):abstr 303.
5. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
6. Kawahara M, Furuse K, Segawa Y, et al; S-1 Cooperative Study Group (Lung Cancer Working Group). Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer* 2001;85:939–943.
7. Ichinose Y, Yoshimori K, Sakai H, et al. S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. *Clin Cancer Res* 2004;10:7860–7864.
8. Kubota K, Sakai H, Yamamoto N, et al. A multi-institution phase I/II trial of triweekly regimen with S-1 plus cisplatin in patients with advanced non-small cell lung cancer. *J Thorac Oncol* 2010;5:702–706.
9. Ichinose Y, Takanashi N, Yano T, et al. A phase II trial of oral tegafur and uracil plus cisplatin in patients with inoperable nonsmall cell lung cancer. *Cancer* 1995;75:2677–2680.
10. Ichinose Y, Yosimori K, Yoneda S, et al. UFT plus cisplatin combination chemotherapy in the treatment of patients with advanced nonsmall cell lung carcinoma: a multiinstitutional phase II trial. *Cancer* 2000;88:318–323.
11. Kubota K, Watanabe K, Kunitoh H, et al; Japanese Taxotere Lung Cancer Study Group. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. *J Clin Oncol* 2004;22:254–261.
12. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007; 18:317–323.
13. Schiller JH, Harrington D, Belani CP, et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
14. Okamoto I, Yoshioka H, Morita S, et al. Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: results of a west Japan oncology group study. *J Clin Oncol* 2010;28:5240–5246.
15. Byfield JE, Calabro-Jones P, Klisak I, et al. Pharmacologic requirements for obtaining sensitization of human tumor cells in vitro to combined 5-Fluorouracil or ftorafur and x rays. *Int J Radiat Oncol Biol Phys* 1982;8:1923–1933.
16. Douple EB, Richmond RC. Enhancement of the potentiation of radiotherapy by platinum drugs in a mouse tumor. *Int J Radiat Oncol Biol Phys* 1982;8:501–503.
17. Gemma A, Kudoh S, Yoshimura A, et al. Pilot trial of a combination comprising of consecutive oral administration of UFT, and two-divided administration of CDDP in non-small cell lung cancer. *Anticancer Res* 1995;15:2691–2695.
18. Koizumi W, Tanabe S, Saigenji K, et al. Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. *Br J Cancer* 2003;89:2207–2212.
19. Fukushima M, Sakamoto K, Sakata M, et al. Gimeracil, a component of S-1, may enhance the antitumor activity of X-ray irradiation in human cancer xenograft models in vivo. *Oncol Rep* 2010;24:1307–1313.
20. Takagi M, Sakata K, Someya M, et al. Gimeracil sensitizes cells to radiation via inhibition of homologous recombination. *Radiother Oncol* 2010;96:259–266.
21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of

the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
22. Vokes EE, Herndon JE II, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002;20:4191–4198.
23. Vokes EE, Herndon JE II, Kelley MJ, et al; Cancer and Leukemia Group B. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol* 2007;25:1698–1704.
24. Hanna N, Neubauer M, Yiannoutsos C, et al; Hoosier Oncology Group; US Oncology. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* 2008;26:5755–5760.
25. Ohyanagi F, Yamamoto N, Horiike A, et al. Phase II trial of S-1 and cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer. *Br J Cancer* 2009;101:225–231.
26. Ichinose Y, Kato H, Koike T, et al; Japanese Clinical Oncology Group. Completely resected stage IIIA non-small cell lung cancer: the significance of primary tumor location and N2 station. *J Thorac Cardiovasc Surg* 2001;122:803–808.
27. Segawa Y, Kiura K, Takigawa N, et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. *J Clin Oncol* 2010;28:3299–3306.
28. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol* 2010;28:3739–3745.

