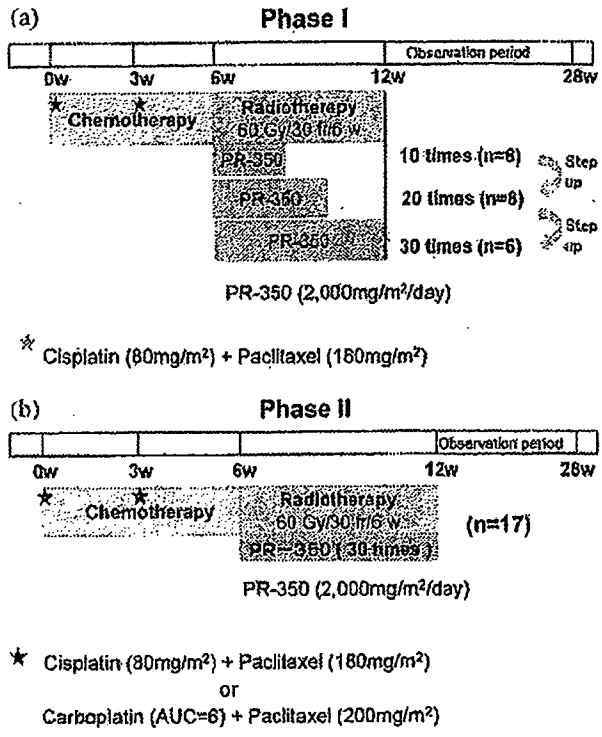

Fig. 1. (a, b) Design of the trial: (a) Phase I portion; (b) Phase II portion.

At the start of this multi-institutional study, three-dimensional treatment planning system using computed tomography was not available at many institutions. Therefore, the protocol for RT was prescribed by a two-dimensional treatment planning techniques, and three-dimensional dose constraints for both planning target volume (PTV) and normal risk organs were not defined in the protocol. The RT doses were specified in the center of the target volume, and calculated assuming tissue homogeneity without correction for lung tissues after the example of Radiation Therapy Oncology Group (RTOG) at that time. No immobilization devices were used, and the position of patients was verified by portal films.

The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was 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 (#2) to subcarinal lymph nodes (#7). The contralateral hilum was not included in CTV1. The supraclavicular areas were not to be treated routinely, but could be treated when supraclavicular nodes were involved. CTV1 included a margin of 1 cm for gross tumor volume (GTV) consisting of the primary tumors and the involved lymph nodes ≥1 cm in the shortest diameter, although no margin was added for lymph node areas without involved nodes. CTV2 included only the primary tumor and the involved lymph nodes with a margin of 0.5 to 1 cm. The PTV margins for CTV were 0.5 to 1 cm. Although field margins for PTV were not determined in the protocol, appropriate field margins were added at each institution. The spinal cord was excluded from the fields for CTV2 by appropriate methods such as the oblique opposing method. Portal films were obtained at the first time of each treatment plan, but weekly verification was not mandatory.

Quality assurance of thoracic RT including review of simulation films, portal films, and RT dose data was conducted throughout the trial by one of the authors (Y.N.). Approximately 90% (33/37) of the patients received thoracic RT consistent with the protocol guidelines. For 2 patients, the RT field was larger than the guidelines allowed, whereas for 2 other patients, margins for target volume were insufficient.

A novel hypoxic cell radiosensitizer, PR-350, developed by POLA Chemical Industries Inc. (Yokohama, Japan), was used. PR-350 (1000 mg) was dissolved in a solution of 50 ml. PR-350 at 2000 mg/m^2 was infused intravenously over 20 to 30 min before thoracic RT daily. Thoracic RT was given within 10 to 40 min of the end of infusion. Among the 770 sessions, violation rates for the duration of infusion and time interval were 5.8% (45/770) and 3.0% (23/770), respectively.

In Phase I, the starting dosage of PR-350 was 10 daily doses in combination with thoracic RT for the first 2 weeks, and the number of administrations of PR-350 was escalated in increments of 10 for successive groups of 6 to 8 new patients to 30 doses over 6 weeks. Dose-limiting toxicities (DLTs) were defined as Grade 4 leucopenia or neutropenia, thrombopenia of <20,000/μL, esophagitis of Grade 4 or more, or other nonhematologic toxicities of Grade 3 or more. When one third or less of 6 to 8 patients showed DLTs, the dosage of PR-350 was raised to the next level.

Venous blood samples were collected before, immediately after, and 1.5, 3, 5, 7, and 24 h after the infusion of PR-350 on the first day and the last day of administration for 4 or 5 patients at each dose level of the Phase I trial and 3 patients in the Phase II trial. PR-350 levels in urine were also measured for 24 h before and after the first infusion, 24 h after the last infusion, and 24–48 h after the last infusion. The concentration of PR-350 in serum and urine samples was analyzed by high-performance liquid chromatography.

Efficacy evaluation

The objectives of this trial were to evaluate a recommended dose of PR-350 in the Phase I portion, and to evaluate the local tumor response rate in the chest (radiation portal), overall survival, and toxicities associated with thoracic RT and PR-350 after induction CT in the Phase I/II portion.

Local tumor response in the radiation portal was evaluated using CT scans obtained at baseline, after each induction CT, at 32 to 40 Gy of thoracic RT, every 4 weeks after the completion of thoracic RT to the 20th week of the RT. Tumor response was determined using World Health Organization Criteria for Reporting Cancer Treatment by extramural evaluation. In this analysis, responses of the two target lesions of primary tumors and mediastinal nodes were evaluated separately. When both target lesions showed a complete response (CR; complete disappearance of all known disease) for more than 4 weeks, local tumor response was scored as CR. On the other hand, when one of the two target lesions showed a partial response (PR; 50% or more decrease in tumor size) for more than 4 weeks and the other target lesion showed CR, PR, or no change (NC; less than 50% decrease, or less than 25% increase in tumor size), local tumor response was scored as PR. When both target lesions showed NC, local tumor response was scored as NC. When one or more target lesions showed progressive disease (PD; a 25% or greater increase in tumor size, or the appearance of new lesions in the radiation portal), local tumor response was scored as PD.

Survival time was defined as the period from the first day of induction CT to death. All patients were followed for a minimum of 24 months. The final date for inclusion of survival data in the analysis was December 1, 2006. Overall survival rates were calculated using the Kaplan-Meier estimates.

RESULTS

Patient characteristics and compliance

A diagram explaining the number of patients enrolled and analyzed is provided in Figure 2. A total of 41 patients with unresectable stage IIIA or IIIB NSCLC from 19 institutions in Japan were enrolled in the first entry from August 2000 to November 2004. During the study period, accrual of patients was stopped several times because of observation period of toxicities for the level I (3 months) and level II (7 months), and revision of the protocol for the Phase II portion (18 months).

Of the 41 patients, 2 patients in the Phase I portion could not enter into the second entry because of bleeding from gastric ulcers during induction CT or withdrawal of consent. In the Phase II portion, 1 patient died of tumor bleeding during induction CT, and induction CT was not indicated for another patient because of glaucoma. Thus, the remaining 37 patients (full analysis set [FAS]) were enrolled into the second entry. Pretreatment characteristics of the FAS are presented in Table 1.

In the first level of the Phase I portion (10 doses of PR-350), DLTs (Grade 3 skin rash and Grade 5 radiation pneumonitis) were noted for 2 patients. In the second level (20 doses), DLT (Grade 5 radiation pneumonitis) was noted for 1 patient. In the third level (30 doses), DLT (Grade 3 skin rash) was noted for 1 patient. Thus, in the Phase II portion ($n = 17$), PR-350 was administered 30 times.

Thoracic RT was terminated before 60 Gy for 4 of the 37 patients because of progressive disease ($n = 2$) and pneumonia ($n = 2$). For 5 patients, full-dose RT of 60 Gy and <70% of the planned PR-350 doses were combined because of acute toxicities ($n = 3$) or patient refusal of PR-350 ($n = 2$). For the remaining 28 patients, PR-350 at 70% or more of the planned dose could be combined with thoracic RT of 60 Gy.

Local response and survival

According to the extramural assessments, CR and PR were achieved by 8% (3/37) and 68% (25/37) of patients, respectively. Thus, the overall response rate (CR+PR) was 76% (28/37). The response rate for patients who received PR-350 21 to 30 doses was 89%, whereas that for those who received 2 to 20 doses was 63%. The difference in tumor response was not significant.

Table 1. Patient and tumor characteristics (full analysis set; $n = 37$)

Gender (men/women)	30/7
Age, y (mean and range)	61.8 (46–74)
PS (0/1)	12/25
Stage (IIIA/IIIB)	8/29
Histology:	
Adenocarcinoma	17
Squamous cell carcinoma	16
Large-cell carcinoma	1
Unclassified carcinoma	3

Figure 3 shows the Kaplan-Meier survival curve for the 37 patients. The median survival time (MST) was 15.9 months, and overall survival rates at 2 and 3 years were 24% and 18%, respectively. The MSTs and survival rates were also analyzed according to clinical stage and actual doses of PR-350. There was no significant difference in the survival rate between stage IIIA ($n = 8$) and stage IIIB ($n = 29$). The MST and 2-year survival rate for 18 patients receiving 21 to 30 doses of PR-350 were 20.9 months and 33%, respectively, whereas those for 19 patients who received 2 to 20 doses were 13.7 months and 16%, respectively (Fig. 4a). However, this trend was not observed when compared with their intended prescribed dose (10 and 20 doses vs. 30 doses) of PR-350 (Fig. 4b). The MST and 2-year survival rate for 14 patients enrolled in the 10 and 20 doses levels were 15.9 months and 21%, respectively, whereas those for 19 patients in the 30 doses level were 14.9 months and 26%, respectively.

Toxicities

Tables 2 and 3 show hematologic and nonhematologic toxicities after the second entry, respectively. A major hematologic toxicity for most patients was lymphopenia.

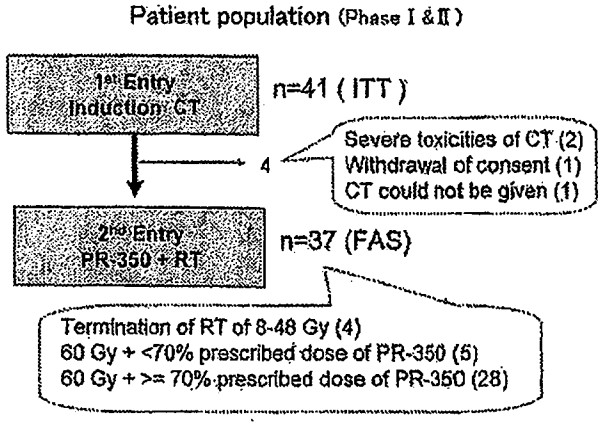

Fig. 2. Patient population in this trial. Of the 41 patients enrolled in the first entry (intention to treat [ITT]), 37 patients were included in the second entry (full analysis set [FAS]).

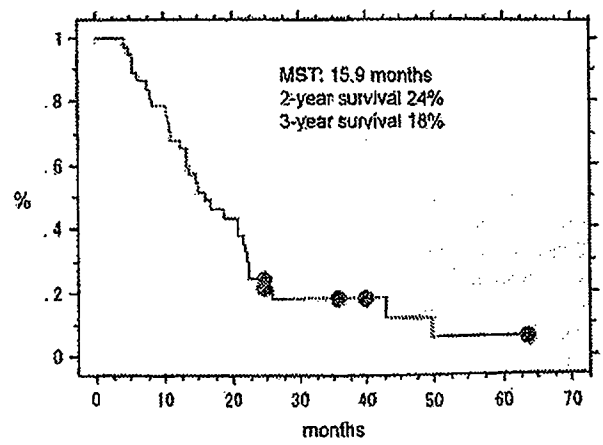

Fig. 3. Overall survival rate for the 37 patients (full analysis set [FAS]). MST = median survival time.

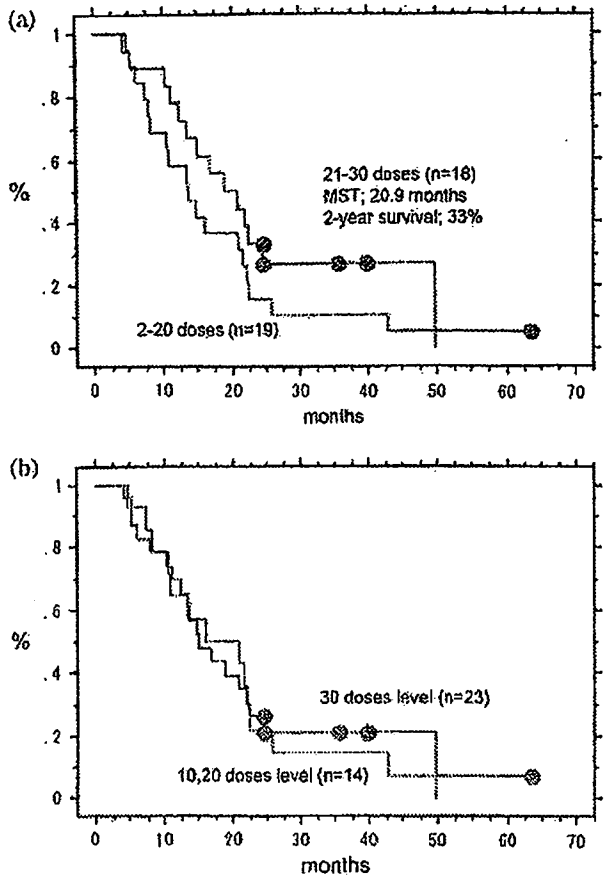

Fig. 4. (a, b) Overall survival rates according to the actual doses of PR-350. No significant difference between the two groups. (b) Overall survival rates according to the intended prescribed doses of PR-350. MST = median survival time.

The incidence of Grade 3 or more lymphopenia was 78%. However, only a few patients showed Grade 3 or more leucopenia or anemia. A major nonhematologic toxicity was radiation pneumonitis, and Grade 3 or more pneumonitis was noted in 6 patients (16%) including the 2 with treatment-related deaths. For 1 of the 2 patients with treatment-related deaths, the initial RT field exceeded one half of the involved lung, which violated the guidelines for RT fields. For the other patient with treatment-related death, extramural review revealed

Table 2. Hematologic toxicities after the second entry (full analysis set; $n = 37$)

Grade of toxicities	G1	G2	G3 or more
Leukocytes	12 (32%)	9 (24%)	2 (5%)
Lymphopenia	0 (0%)	6 (16%)	29 (78%)
Neutrophils	6 (16%)	9 (24%)	1 (3%)
Hemoglobin	2 (5%)	12 (32%)	3 (8%)
Platelets	11 (30%)	0 (0%)	1 (3%)
AST	9 (24%)	1 (3%)	1 (3%)
ALT	9 (24%)	3 (8%)	2 (5%)
Creatinine	1 (3%)	0 (0%)	0 (0%)

Table 3. Nonhematologic toxicities after the second entry (full analysis set; $n = 37$)

Grade of toxicities	G1	G2	G3 or more
Radiation pneumonitis	7 (19%)	5 (14%)	6* (16%)
Skin rash	5 (14%)	3 (8%)	3 (8%)
Peripheral neuropathy	9 (24%)	0 (0%)	0 (0%)
Radiation dermatitis	18 (49%)	4 (11%)	0 (0%)
Dysphagia/esophagitis	25 (68%)	6 (16%)	0 (0%)
Febrile neutropenia	0 (0%)	0 (0%)	1 (3%)
Edema	3 (8%)	1 (3%)	1 (3%)

* Two patients with treatment-related deaths were included.

apparent pulmonary fibrosis on his chest radiography before treatment, which was a violation of the eligibility criteria.

During induction CT, Grade 1 or 2 peripheral neuropathy was observed in 26 patients, and at the start of second entry 17 patients (46%) had only Grade 1 peripheral neuropathy. After the second entry, Grade 1 peripheral neuropathy was prolonged for 3 of the 17 patients. Newly developed peripheral neuropathy of Grade 1 was noted in 6 patients. In total, peripheral neuropathy of Grade 1 was noted in 9 patients (24%). Allergic skin rash of Grade 3 or less was observed in 11 patients (30%). Skin rash was seen out of RT field, and scored differently from radiation dermatitis. Notably, no Grade 3 or more esophageal toxicity was noted.

Pharmacokinetic study

Figure 5 shows changes in the serum concentration of PR-350 in the first and the last sessions. After both sessions, PR-350 was rapidly cleared by the kidney, and no accumulation was observed even after the 30th session. Similarly, no cumulative effect was demonstrated after the 10th and 20th sessions (data not shown).

DISCUSSION

In the Phase I portion of this trial, thoracic RT combined with 30 daily administrations of PR-350 at 2000 mg/m^2 after induction CT was well tolerated. As a single dose or five daily doses of PR-350 at 2000 mg/m^2 has been shown to be safe in previous clinical trials (18, 19), dose escalation

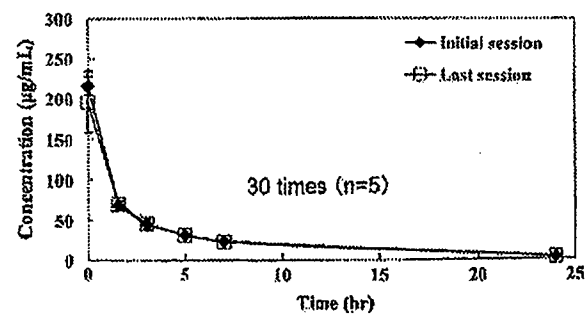

Fig. 5. Changes in serum concentration of PR-350 in the first and the last (30th) session. Means and standard errors are shown. PR-350 was rapidly cleared in both sessions, and no accumulation of PR-350 was observed in the 30th session.

was started from 10 doses of PR-350 in this study. As DLTs, radiation pneumonitis or skin rash of Grade 3 or more was noted in one third or less of 6 to 8 patients at each level, and so 30 daily administrations of PR-350 at 2000 mg/m^2 was determined as the recommended dosage in the Phase II portion of the trial.

A major hematologic toxicity was lymphopenia, although other hematologic toxicities were mild (Table 3). A major nonhematologic toxicity was radiation pneumonitis including two patients with TRD. Grade 3 or higher radiation pneumonitis was observed in 6 patients (16%). A similar rate of radiation pneumonitis is reported by a retrospective study at the National Cancer Center Hospital in Japan (20). In that analysis, severe radiation pneumonitis of Grade 3 or more was noted in 13% of 191 patients with lung cancer treated by CRT or RT alone between 1988 and 1998 (20). On the other hand, a less than 2% incidence of Grade 3 or higher pulmonary toxicity was reported for both sequential and concurrent CRT groups in a Japanese Phase III trial for locally advanced NSCLC using the same eligibility criterion on RT fields (6). It is unclear why pulmonary toxicity in the trial was so low. However the low total RT dose of 56 Gy may have contributed to that.

Because 3D RT planning was not available, it was impossible to correlate toxicity parameters with dose–volume histogram (DVH) information in this study. Although it can not be excluded that PR-350 enhances the effects of radiation on normal lung tissues, we consider that the relatively high incidence of radiation pneumonitis is attributable to our former two-dimensional RT technique. Extramural review of RT films revealed that two TRDs might have been attributable to a violation of protocol guidelines for RT fields or a violation of eligibility criteria on pulmonary disease. To evaluate the effect of PR-350 on radiation pneumonitis, an additional Phase II trial with a three-dimensional RT method may be required.

Neither Grade 3 or more esophageal toxicity, nor Grade 2 or more peripheral neuropathy, was noted. In the PK study, no accumulative effect was observed even after the 30th dose (Fig. 5). The major limitation of 2-nitroimidazoles including misonidazole and ethanidazole is neuropathy (10–12, 21, 22). For head-and-neck cancer, randomized clinical trials comparing RT plus ethanidazole and RT alone have been reported (21, 22). In these trials, ethanidazole at 2000 mg/m^2 given three times weekly for 17 doses was combined with RT, and peripheral neuropathy of Grade 1 to 3 was noted in 24% to 28% of patients. In the present trial, PR-350 at 2000 mg/m^2 was given five times weekly for 10 to 30 doses, and only peripheral neuropathy of Grade 1 was noted in 24% of patients. Thus, PR-350 is apparently less neurotoxic than ethanidazole.

The overall response rate in the RT field was 76% (28/37). For patients who received 21 to 30 doses of PR-350, the overall response rate was as high as 89%. The MST and 2-year survival rate for FAS were 15.9 months and 24%, respectively. This result is well in the range of values for sequential CRT for locally advanced NSCLC (3, 6, 7). In the FAS, patients treated with suboptimal doses of PR-350 (10 or 20 doses) were included in the Phase I portion. Although the analysis according to the intended prescribed doses of PR-350 did not show the difference in survival rate (Fig. 4b), the MST and 2-year survival rate for 18 patients actually receiving 21 to 30 doses of PR-350 were 20.9 months and 33%, respectively (Fig. 4a). These values are well compatible with those for concurrent CRT (6, 7). This Phase II result is promising because a survival rate similar to that for concurrent CRT was obtained by daily administration of PR-350 with an incidence of acute toxicities as low as that for sequential CRT.

At present, concurrent CRT is the standard treatment for locally advanced NSCLC. However, acute toxicities are inevitably more common during concurrent CRT (4–7). So, concurrent CRT is not recommended for elderly patients or patients with a poor performance status. The low incidence of hematologic toxicities and radiation esophagitis in this study has special significance for these patients. The results of this Phase I/II study support the hypothesis that adding PR-350 to sequential CRT may decrease the rate of local recurrence without a significant increase in toxicity. Similarly, a promising clinical result obtained by adding a radiosensitizer, efaproxiral, to sequential CRT has been reported (23). Therefore, the present strategy of sequential CRT combined with PR-350 is a promising approach for locally advanced NSCLC, and a randomized study should be pursued. Furthermore, PR-350 may also be an ideal candidate for incorporation into concurrent CRT, as it could potentially increase the efficacy of concurrent CRT without increasing the toxicities.

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CLINICAL INVESTIGATION **Lung**

PHASE I/II TRIAL OF SEQUENTIAL CHEMORADIOTHERAPY USING A NOVEL HYPOXIC CELL RADIOSENSITIZER, DORANIDAZOLE (PR-350), IN PATIENTS WITH LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER (WJTOG-0002)

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Purpose: This Phase I/II trial was conducted to assess the efficacy and safety of PR-350, a novel hypoxic cell radiosensitizer, when administered with thoracic radiation therapy (RT) after induction chemotherapy (CT) for locally advanced non–small-cell lung cancer (NSCLC).

Methods and Materials: Two cycles of cisplatin (80 mg/m^2) and paclitaxel (180 mg/m^2), or carboplatin (AUC = 6) and paclitaxel (200 mg/m^2) were given before RT of 60 Gy in 30 fractions. In the Phase I portion, the starting dosage of PR-350 was 10 daily administrations (2000 mg/m^2) in combination with RT, and this number was increased in increments of 10 for successive groups to 30 doses.

Results: In total, 37 patients were enrolled. In Phase I (n = 20), PR-350 could be administered 30 times with concurrent thoracic RT. Thus, in Phase II (n = 17), PR-350 was administered 30 times. The major toxicity was radiation pneumonitis, with Grade 3 or more pneumonitis noted in 6 patients (16%) including 2 with treatment-related deaths. However, no Grade 3 or more esophageal toxicity was noted, and only Grade 1 peripheral neuropathy was noted in 9 patients (24%). For all 37 patients, the median survival time (MST) and the 2-year survival rate were 15.9 months and 24%, respectively. For 18 patients receiving 21 to 30 doses of PR-350, the MST and 2-year survival rate were 20.9 months and 33%, respectively.

Conclusions: Thoracic RT combined with 30 daily administrations of PR-350 after induction CT was well tolerated and promising for locally advanced NSCLC.

Hypoxic cell radiosensitizer, Doranidazole, Non–small-cell lung cancer, Clinical trial, Chemoradiation.

INTRODUCTION

The standard treatment for patients with locally advanced non–small-cell lung cancer (NSCLC) has become combined chemotherapy (CT) and radiotherapy (RT). Induction CT before thoracic RT is effective for patients with locally advanced NSCLC, as many such patients have micrometastatic disease at presentation and ultimately develop metastatic disease (1–4). However, induction CT did not improve the local control rate by thoracic RT (3, 4). To obtain long-term survival for the patients, adequate loco-regional control by thoracic RT is essential. Improved loco-regional control and survival rates have been achieved clinically with the concurrent use of CT and RT for locally

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Conflict of interest: Y. Nishimura, M. Fukuoka, and Y. Ariyoshi are consultants to POLA Chemical Industries Inc.

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advanced NSCLC (4–7). At present, concurrent chemoradiotherapy (CRT) is the standard treatment for locally advanced NSCLC. However, acute toxicities are inevitably increased during concurrent CRT (4–7). Because hematologic and gastrointestinal toxicities are significantly more common during concurrent CRT than for RT alone or sequential CRT, concurrent CRT is not recommended for elderly patients or patients with a poor performance status.

Hypoxic cells are 2.5 to 3.0 times less sensitive to radiation than well-oxygenated cells (4, 8, 9). Tumors often include hypoxic areas, which are a cause of radioresistance. One approach to conquering hypoxic cells is the use of hypoxic cell radiosensitizers. These drugs mimic the effect of oxygen by increasing radiation damage. Nitroimidazoles such as misonidazole and ethanidazole are highly effective at enhancing the radioresponsiveness of tumors in rodents (4, 8–12). A meta-analysis of 50 randomized clinical trials showed that modifications of tumor hypoxia significantly improve the loco-regional tumor control and overall survival achieved with RT (11). Depending on the site of the tumor, treatment benefits can be observed for head and neck tumors as well as bladder tumors (11–13). A randomized clinical trial performed by the Danish Head and Neck Cancer Study group showed that a hypoxic radiosensitizer, nimorazole, improved loco-regional control in head-and-neck cancer as well as a reduction of cancer-related deaths significantly (13). Based on this positive result, the use of nimorazole becomes standard practice for head and neck cancer in Denmark (12). However, no significant improvement by a hypoxic cell sensitizer has been found for lung cancer.

PR-350, a 2-nitroimidazole nucleoside analog doranidazole, is characterized by a very low level of toxicity, with the 50% lethal dose in mice exceeding 5 g/kg, but an efficiency similar to that of ethanidazole (14–17). In a Phase I trial, no neurotoxicity was observed when PR-350 was administered for 5 consecutive days at a daily dose of 800–2000 mg/m^2 in combination with external RT for various cancers (18). Thereafter, the efficacy of PR-350 combined with intraoperative RT for locally advanced pancreatic cancer was tested in a randomized trial (19). PR-350 (2000 mg/m^2) or placebo was infused immediately before intraoperative RT (25 Gy) in a total of 47 patients. Both groups received postoperative external RT (40 Gy/20 fractions) without CT. No significant difference in the overall survival rate was found between the two groups. However, the 2-year survival rate was 18% for the PR-350 group and 4% for the control group, suggesting that PR-350 improves the long-term local control rate.

Because local control remains a problem for patients with locally advanced NSCLC, PR-350 was added to a sequential CRT regimen in an attempt to improve local control, while maintaining the lower toxicity rate compared with concurrent CRT. This Phase I/II trial was conducted to assess the efficacy, safety, and pharmacokinetics (PK) of PR-350 when administered for 10 to 30 days at a daily dose of 2000 mg/m^2 combined with conventional thoracic RT after induction CT for treatment of locally advanced NSCLC.

METHODS AND MATERIALS

Investigational design

This was a Phase I/II, nonrandomized, multicenter study conducted by the West Japan Thoracic Oncology Group (WJTOG) in compliance with Good Clinical Practice guidelines. The protocol was approved by the institutional review boards or ethics committees of all participating institutions, and written informed consent was obtained twice, before induction CT at the first entry and before thoracic RT combined with PR-350 at the second entry.

Patient eligibility

The pretreatment staging work-up included medical history, physical examination, complete blood count, biochemical screening tests, chest radiography, bronchoscopy, computed tomography of the thorax and upper abdomen. Brain CT or MRI, as well as bone scans were performed whenever possible. Positron emission tomography (PET) was not performed because health insurance did not cover PET at that time. Mediastinal lymph nodes of more than 10 mm in the shortest diameter were regarded as malignant nodes, and histologic proof of N2 or N3 status was not required.

Major eligibility criteria at the first entry included 20–74 years old, histologically, or cytologically proven NSCLC, surgically unresectable stage IIIA and IIIB, no prior therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and adequate organ functions. Patients with severe emphysema, chronic bronchitis, or apparent findings of pulmonary fibrosis or interstitial pneumonitis on chest radiography were excluded.

Major eligibility criteria at the second entry included an ECOG performance status of 0 to 2, a white blood cell (WBC) count of ≥3,000/μL, a platelet count of ≥75,000/μL, a creatinine level of <1.5 mg/dL, a PaO_2 level of ≥70 mm Hg, a percent diffusion lung carbon monoxide ($\%D_{LCO}$) level of ≥60, and neuropathy of Grade 0 or Grade 1. In addition, patients whose RT field exceeded one half of the involved lung were excluded. Although this eligibility criterion on the RT field was relatively subjective and obscure, it was commonly used in Japanese clinical trials for NSCLC to exclude large thoracic RT fields (6).

Treatment plan

Figure 1 provides the design of the Phase I and Phase II portions. In the Phase I trial, patients received two cycles of induction CT consisting of cisplatin at 80 mg/m^2 and paclitaxel at 180 mg/m^2. Induction CT was repeated 3 weeks later. Induction CT with carboplatin (AUC = 6) and paclitaxel (200 mg/m^2) and a 3-week interval was also permitted in the Phase II portion. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 2.0. Treatment could be delayed no more than 2 weeks to allow recovery from toxicity. Dose adjustments of CT for toxicity were made according to guidelines stipulated in the protocol.

Thoracic RT combined with PR-350 was begun 3 to 5 weeks after completion of the induction CT when patients agreed to the protocol and fulfilled the second entry criteria. All patients were treated with a linear accelerator photon beam of 4 MV or more. The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over 6 weeks.

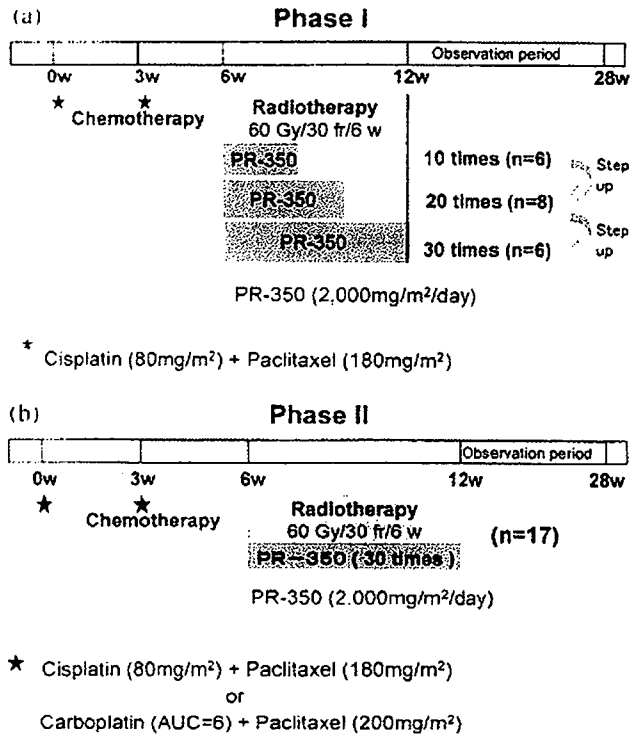

Fig. 1. (a, b) Design of the trial: (a) Phase I portion; (b) Phase II portion.

At the start of this multi-institutional study, three-dimensional treatment planning system using computed tomography was not available at many institutions. Therefore, the protocol for RT was prescribed by a two-dimensional treatment planning techniques, and three-dimensional dose constraints for both planning target volume (PTV) and normal risk organs were not defined in the protocol. The RT doses were specified in the center of the target volume, and calculated assuming tissue homogeneity without correction for lung tissues after the example of Radiation Therapy Oncology Group (RTOG) at that time. No immobilization devices were used, and the position of patients was verified by portal films.

The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was 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 (#2) to subcarinal lymph nodes (#7). The contralateral hilum was not included in CTV1. The supraclavicular areas were not to be treated routinely, but could be treated when supraclavicular nodes were involved. CTV1 included a margin of 1 cm for gross tumor volume (GTV) consisting of the primary tumors and the involved lymph nodes ≥1 cm in the shortest diameter, although no margin was added for lymph node areas without involved nodes. CTV2 included only the primary tumor and the involved lymph nodes with a margin of 0.5 to 1 cm. The PTV margins for CTV were 0.5 to 1 cm. Although field margins for PTV were not determined in the protocol, appropriate field margins were added at each institution. The spinal cord was excluded from the fields for CTV2 by appropriate methods such as the oblique opposing method. Portal films were obtained at the first time of each treatment plan, but weekly verification was not mandatory.

Quality assurance of thoracic RT including review of simulation films, portal films, and RT dose data was conducted throughout the trial by one of the authors (Y.N.). Approximately 90% (33/37) of the patients received thoracic RT consistent with the protocol guidelines. For 2 patients, the RT field was larger than the guidelines allowed, whereas for 2 other patients, margins for target volume were insufficient.

A novel hypoxic cell radiosensitizer, PR-350, developed by POLA Chemical Industries Inc. (Yokohama, Japan), was used. PR-350 (1000 mg) was dissolved in a solution of 50 ml. PR-350 at 2000 mg/m^2 was infused intravenously over 20 to 30 min before thoracic RT daily. Thoracic RT was given within 10 to 40 min of the end of infusion. Among the 770 sessions, violation rates for the duration of infusion and time interval were 5.8% (45/770) and 3.0% (23/770), respectively.

In Phase I, the starting dosage of PR-350 was 10 daily doses in combination with thoracic RT for the first 2 weeks, and the number of administrations of PR-350 was escalated in increments of 10 for successive groups of 6 to 8 new patients to 30 doses over 6 weeks. Dose-limiting toxicities (DLTs) were defined as Grade 4 leucopenia or neutropenia, thrombopenia of <20,000/μL, esophagitis of Grade 4 or more, or other nonhematologic toxicities of Grade 3 or more. When one third or less of 6 to 8 patients showed DLTs, the dosage of PR-350 was raised to the next level.

Venous blood samples were collected before, immediately after, and 1.5, 3, 5, 7, and 24 h after the infusion of PR-350 on the first day and the last day of administration for 4 or 5 patients at each dose level of the Phase I trial and 3 patients in the Phase II trial. PR-350 levels in urine were also measured for 24 h before and after the first infusion, 24 h after the last infusion, and 24–48 h after the last infusion. The concentration of PR-350 in serum and urine samples was analyzed by high-performance liquid chromatography.

Efficacy evaluation

The objectives of this trial were to evaluate a recommended dose of PR-350 in the Phase I portion, and to evaluate the local tumor response rate in the chest (radiation portal), overall survival, and toxicities associated with thoracic RT and PR-350 after induction CT in the Phase I/II portion.

Local tumor response in the radiation portal was evaluated using CT scans obtained at baseline, after each induction CT, at 32 to 40 Gy of thoracic RT, every 4 weeks after the completion of thoracic RT to the 20th week of the RT. Tumor response was determined using World Health Organization Criteria for Reporting Cancer Treatment by extramural evaluation. In this analysis, responses of the two target lesions of primary tumors and mediastinal nodes were evaluated separately. When both target lesions showed a complete response (CR; complete disappearance of all known disease) for more than 4 weeks, local tumor response was scored as CR. On the other hand, when one of the two target lesions showed a partial response (PR; 50% or more decrease in tumor size) for more than 4 weeks and the other target lesion showed CR, PR, or no change (NC; less than 50% decrease, or less than 25% increase in tumor size), local tumor response was scored as PR. When both target lesions showed NC, local tumor response was scored as NC. When one or more target lesions showed progressive disease (PD; a 25% or greater increase in tumor size, or the appearance of new lesions in the radiation portal), local tumor response was scored as PD.

Survival time was defined as the period from the first day of induction CT to death. All patients were followed for a minimum of 24 months. The final date for inclusion of survival data in the analysis was December 1, 2006. Overall survival rates were calculated using the Kaplan-Meier estimates.

RESULTS

Patient characteristics and compliance

A diagram explaining the number of patients enrolled and analyzed is provided in Figure 2. A total of 41 patients with unresectable stage IIIA or IIIB NSCLC from 19 institutions in Japan were enrolled in the first entry from August 2000 to November 2004. During the study period, accrual of patients was stopped several times because of observation period of toxicities for the level I (3 months) and level II (7 months), and revision of the protocol for the Phase II portion (18 months).

Of the 41 patients, 2 patients in the Phase I portion could not enter into the second entry because of bleeding from gastric ulcers during induction CT or withdrawal of consent. In the Phase II portion, 1 patient died of tumor bleeding during induction CT, and induction CT was not indicated for another patient because of glaucoma. Thus, the remaining 37 patients (full analysis set [FAS]) were enrolled into the second entry. Pretreatment characteristics of the FAS are presented in Table 1.

In the first level of the Phase I portion (10 doses of PR-350), DLTs (Grade 3 skin rash and Grade 5 radiation pneumonitis) were noted for 2 patients. In the second level (20 doses), DLT (Grade 5 radiation pneumonitis) was noted for 1 patient. In the third level (30 doses), DLT (Grade 3 skin rash) was noted for 1 patient. Thus, in the Phase II portion (n = 17), PR-350 was administered 30 times.

Thoracic RT was terminated before 60 Gy for 4 of the 37 patients because of progressive disease (n = 2) and pneumonia (n = 2). For 5 patients, full-dose RT of 60 Gy and <70% of the planned PR-350 doses were combined because of acute toxicities (n = 3) or patient refusal of PR-350 (n = 2). For the remaining 28 patients, PR-350 at 70% or more of the planned dose could be combined with thoracic RT of 60 Gy.

Local response and survival

According to the extramural assessments, CR and PR were achieved by 8% (3/37) and 68% (25/37) of patients, respectively. Thus, the overall response rate (CR+PR) was 76% (28/37). The response rate for patients who received PR-350 21 to 30 doses was 89%, whereas that for those who received 2 to 20 doses was 63%. The difference in tumor response was not significant.

Table 1. Patient and tumor characteristics (full analysis set: n = 37)

Gender (men/women)	30/7
Age, y (mean and range)	61.8 (46–74)
PS (0/1)	12/25
Stage (IIIA/IIIB)	8/29
Histology:	
Adenocarcinoma	17
Squamous cell carcinoma	16
Large-cell carcinoma	1
Unclassified carcinoma	3

Figure 3 shows the Kaplan-Meier survival curve for the 37 patients. The median survival time (MST) was 15.9 months, and overall survival rates at 2 and 3 years were 24% and 18%, respectively. The MSTs and survival rates were also analyzed according to clinical stage and actual doses of PR-350. There was no significant difference in the survival rate between stage IIIA (n = 8) and stage IIIB (n = 29). The MST and 2-year survival rate for 18 patients receiving 21 to 30 doses of PR-350 were 20.9 months and 33%, respectively, whereas those for 19 patients who received 2 to 20 doses were 13.7 months and 16%, respectively (Fig. 4a). However, this trend was not observed when compared with their intended prescribed dose (10 and 20 doses vs. 30 doses) of PR-350 (Fig. 4b). The MST and 2-year survival rate for 14 patients enrolled in the 10 and 20 doses levels were 15.9 months and 21%, respectively, whereas those for 19 patients in the 30 doses level were 14.9 months and 26%, respectively.

Toxicities

Tables 2 and 3 show hematologic and nonhematologic toxicities after the second entry, respectively. A major hematologic toxicity for most patients was lymphopenia.

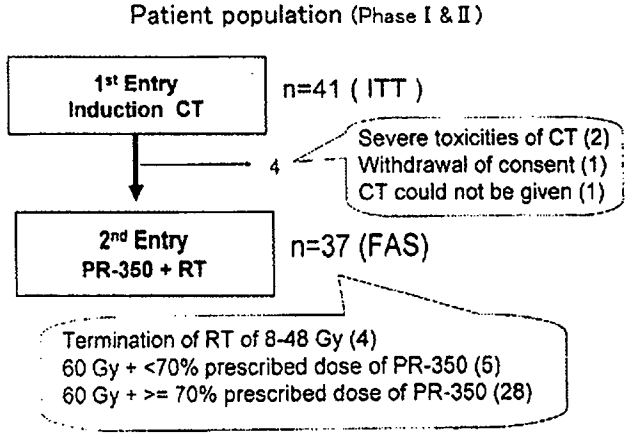

Fig. 2. Patient population in this trial. Of the 41 patients enrolled in the first entry (intention to treat [ITT]), 37 patients were included in the second entry (full analysis set [FAS]).

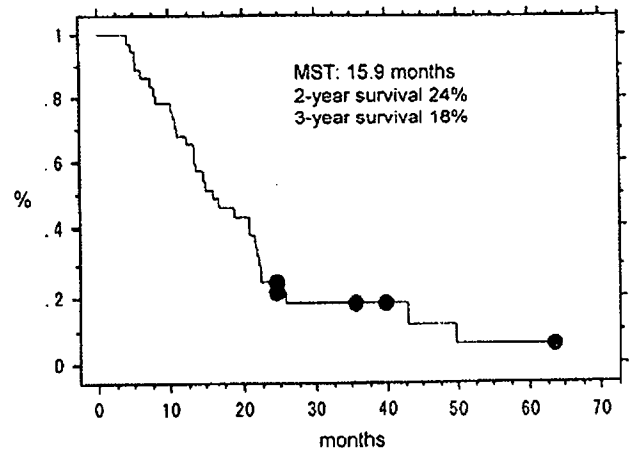

Fig. 3. Overall survival rate for the 37 patients (full analysis set [FAS]). MST = median survival time.

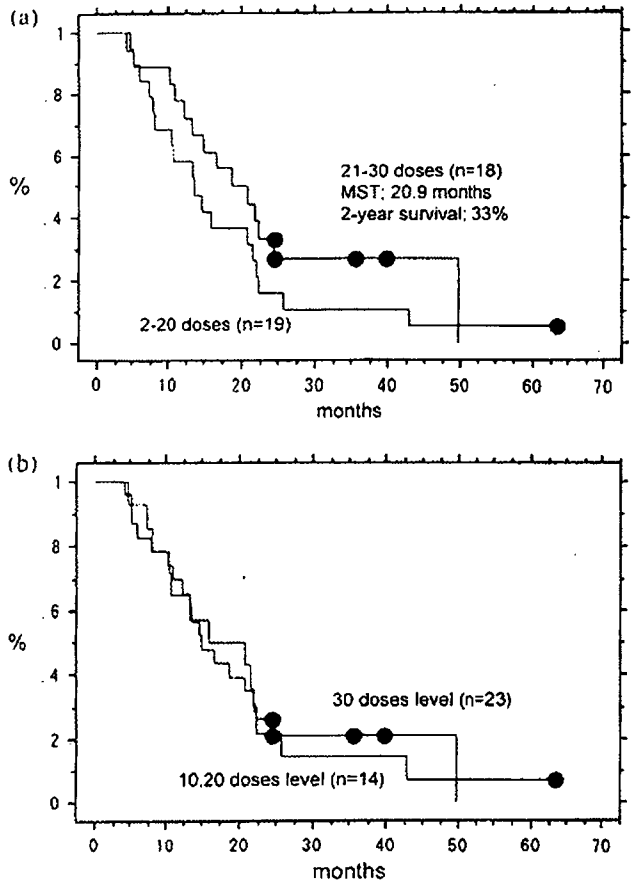

Fig. 4. (a, b) Overall survival rates according to the actual doses of PR-350. No significant difference between the two groups. (b) Overall survival rates according to the intended prescribed doses of PR-350. MST = median survival time.

The incidence of Grade 3 or more lymphopenia was 78%. However, only a few patients showed Grade 3 or more leucopenia or anemia. A major nonhematologic toxicity was radiation pneumonitis, and Grade 3 or more pneumonitis was noted in 6 patients (16%) including the 2 with treatment-related deaths. For 1 of the 2 patients with treatment-related deaths, the initial RT field exceeded one half of the involved lung, which violated the guidelines for RT fields. For the other patient with treatment-related death, extramural review revealed

Table 2. Hematologic toxicities after the second entry (full analysis set; $n = 37$)

Grade of toxicities	G1	G2	G3 or more
Leukocytes	12 (32%)	9 (24%)	2 (5%)
Lymphopenia	0 (0%)	6 (16%)	29 (78%)
Neutrophils	6 (16%)	9 (24%)	1 (3%)
Hemoglobin	2 (5%)	12 (32%)	3 (8%)
Platelets	11 (30%)	0 (0%)	1 (3%)
AST	9 (24%)	1 (3%)	1 (3%)
ALT	9 (24%)	3 (8%)	2 (5%)
Creatinine	1 (3%)	0 (0%)	0 (0%)

Table 3. Nonhematologic toxicities after the second entry (full analysis set; $n = 37$)

Grade of toxicities	G1	G2	G3 or more
Radiation pneumonitis	7 (19%)	5 (14%)	6* (16%)
Skin rash	5 (14%)	3 (8%)	3 (8%)
Peripheral neuropathy	9 (24%)	0 (0%)	0 (0%)
Radiation dermatitis	18 (49%)	4 (11%)	0 (0%)
Dysphagia/esophagitis	25 (68%)	6 (16%)	0 (0%)
Febrile neutropenia	0 (0%)	0 (0%)	1 (3%)
Edema	3 (8%)	1 (3%)	1 (3%)

* Two patients with treatment-related deaths were included.

apparent pulmonary fibrosis on his chest radiography before treatment, which was a violation of the eligibility criteria.

During induction CT, Grade 1 or 2 peripheral neuropathy was observed in 26 patients, and at the start of second entry 17 patients (46%) had only Grade 1 peripheral neuropathy. After the second entry, Grade 1 peripheral neuropathy was prolonged for 3 of the 17 patients. Newly developed peripheral neuropathy of Grade 1 was noted in 6 patients. In total, peripheral neuropathy of Grade 1 was noted in 9 patients (24%). Allergic skin rash of Grade 3 or less was observed in 11 patients (30%). Skin rash was seen out of RT field, and scored differently from radiation dermatitis. Notably, no Grade 3 or more esophageal toxicity was noted.

Pharmacokinetic study

Figure 5 shows changes in the serum concentration of PR-350 in the first and the last sessions. After both sessions, PR-350 was rapidly cleared by the kidney, and no accumulation was observed even after the 30th session. Similarly, no cumulative effect was demonstrated after the 10th and 20th sessions (data not shown).

DISCUSSION

In the Phase I portion of this trial, thoracic RT combined with 30 daily administrations of PR-350 at 2000 mg/m^2 after induction CT was well tolerated. As a single dose or five daily doses of PR-350 at 2000 mg/m^2 has been shown to be safe in previous clinical trials (18, 19), dose escalation

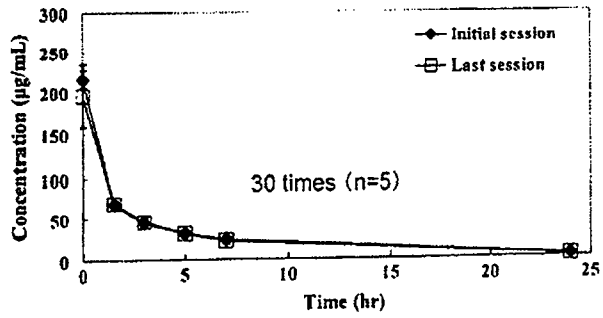

Fig. 5. Changes in serum concentration of PR-350 in the first and the last (30th) session. Means and standard errors are shown. PR-350 was rapidly cleared in both sessions, and no accumulation of PR-350 was observed in the 30th session.

was started from 10 doses of PR-350 in this study. As DLTs, radiation pneumonitis or skin rash of Grade 3 or more was noted in one third or less of 6 to 8 patients at each level, and so 30 daily administrations of PR-350 at 2000 mg/m^2 was determined as the recommended dosage in the Phase II portion of the trial.

A major hematologic toxicity was lymphopenia, although other hematologic toxicities were mild (Table 3). A major nonhematologic toxicity was radiation pneumonitis including two patients with TRD. Grade 3 or higher radiation pneumonitis was observed in 6 patients (16%). A similar rate of radiation pneumonitis is reported by a retrospective study at the National Cancer Center Hospital in Japan (20). In that analysis, severe radiation pneumonitis of Grade 3 or more was noted in 13% of 191 patients with lung cancer treated by CRT or RT alone between 1988 and 1998 (20). On the other hand, a less than 2% incidence of Grade 3 or higher pulmonary toxicity was reported for both sequential and concurrent CRT groups in a Japanese Phase III trial for locally advanced NSCLC using the same eligibility criterion on RT fields (6). It is unclear why pulmonary toxicity in the trial was so low. However the low total RT dose of 56 Gy may have contributed to that.

Because 3D RT planning was not available, it was impossible to correlate toxicity parameters with dose–volume histogram (DVH) information in this study. Although it can not be excluded that PR-350 enhances the effects of radiation on normal lung tissues, we consider that the relatively high incidence of radiation pneumonitis is attributable to our former two-dimensional RT technique. Extramural review of RT films revealed that two TRDs might have been attributable to a violation of protocol guidelines for RT fields or a violation of eligibility criteria on pulmonary disease. To evaluate the effect of PR-350 on radiation pneumonitis, an additional Phase II trial with a three-dimensional RT method may be required.

Neither Grade 3 or more esophageal toxicity, nor Grade 2 or more peripheral neuropathy, was noted. In the PK study, no accumulative effect was observed even after the 30th dose (Fig. 5). The major limitation of 2-nitroimidazoles including misonidazole and ethanidazole is neuropathy (10–12, 21, 22). For head-and-neck cancer, randomized clinical trials comparing RT plus ethanidazole and RT alone have been reported (21, 22). In these trials, ethanidazole at 2000 mg/m^2 given three times weekly for 17 doses was combined with RT, and peripheral neuropathy of Grade 1 to 3 was noted in 24% to 28% of patients. In the present trial, PR-350 at 2000 mg/m^2 was given five times weekly for 10 to 30 doses, and only peripheral neuropathy of Grade 1 was noted in 24% of patients. Thus, PR-350 is apparently less neurotoxic than ethanidazole.

The overall response rate in the RT field was 76% (28/37). For patients who received 21 to 30 doses of PR-350, the overall response rate was as high as 89%. The MST and 2-year survival rate for FAS were 15.9 months and 24%, respectively. This result is well in the range of values for sequential CRT for locally advanced NSCLC (3, 6, 7). In the FAS, patients treated with suboptimal doses of PR-350 (10 or 20 doses) were included in the Phase I portion. Although the analysis according to the intended prescribed doses of PR-350 did not show the difference in survival rate (Fig. 4b), the MST and 2-year survival rate for 18 patients actually receiving 21 to 30 doses of PR-350 were 20.9 months and 33%, respectively (Fig. 4a). These values are well compatible with those for concurrent CRT (6, 7). This Phase II result is promising because a survival rate similar to that for concurrent CRT was obtained by daily administration of PR-350 with an incidence of acute toxicities as low as that for sequential CRT.

At present, concurrent CRT is the standard treatment for locally advanced NSCLC. However, acute toxicities are inevitably more common during concurrent CRT (4–7). So, concurrent CRT is not recommended for elderly patients or patients with a poor performance status. The low incidence of hematologic toxicities and radiation esophagitis in this study has special significance for these patients. The results of this Phase I/II study support the hypothesis that adding PR-350 to sequential CRT may decrease the rate of local recurrence without a significant increase in toxicity. Similarly, a promising clinical result obtained by adding a radiosensitizer, efaproxiral, to sequential CRT has been reported (23). Therefore, the present strategy of sequential CRT combined with PR-350 is a promising approach for locally advanced NSCLC, and a randomized study should be pursued. Furthermore, PR-350 may also be an ideal candidate for incorporation into concurrent CRT, as it could potentially increase the efficacy of concurrent CRT without increasing the toxicities.

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PHASE II STUDIES

Phase II study of amrubicin, 9-amino-anthracycline, in patients with advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group (WJTOG) study

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Summary *Purpose:* We conducted a multicenter phase II study of amrubicin, a novel 9-aminoanthracycline, to evaluate its efficacy and safety in patients with non-small-cell lung cancer (NSCLC). *Patients and methods:* Entry requirements included cytologically or histologically proven measurable NSCLC, stage III or IV, no prior therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate organ function.

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Amrubicin was given by daily intravenous injection at 45 mg/m^2/day for three consecutive days, repeated at 3 week intervals. Each patient received at least three treatment cycles. *Results:* Sixty-two patients were enrolled in this study. Of the 62 registered patients, 60 were eligible and assessable for efficacy, and 59 for toxicity. Overall response rate was 18.3% (95% confidence interval [CI], 9.5 to 30.4%) and median survival time was 8.2 months (95% CI, 6.7 to 10.4 months). Major toxicity was myelosuppression, with incidences of grade 3 or 4 toxicity of 78.0% for neutropenia, 54.2% for leukopenia, 30.5% for anemia, and 28.8% for thrombocytopenia. Non-hematological toxicities with a greater than 50% incidence were anorexia (69.5%), nausea/vomiting (55.9%), and alopecia (75.9%), but were relatively mild, with grade 3 toxicities observed in only one patient each (1.7%). *Conclusion:* Amrubicin was an active, well-tolerated agent in the treatment of NSCLC.

Keywords Amrubicin · Anthracycline · Non-small-cell lung cancer · Phase II study

Introduction

Non-small-cell lung cancer (NSCLC) is already a leading cause of cancer-related deaths worldwide, with an incidence which is increasing. Current therapeutic options are unsatisfactory, however, and development of novel, more effective antitumor agents has been sought.

Amrubicin is a novel, totally synthetic 9-aminoanthracycline, (+)-(7S,9S)-9-acetyl-9-amino-7-[(2-deoxy-β-D-*erythro*-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione hydrochloride, with a similar structure to doxorubicin (Fig. 1) [1].

An important characteristic of amrubicin is that it is a prodrug which is converted to the active metabolite, amrubicinol, via reduction of its C-13 ketone group to a hydroxy group by carbonyl reductase [2]. *In vitro* studies have shown that the cytotoxic activity of amrubicinol is 20 to 220 times more potent than that of its parent compound, amrubicin, and has closely similar potency to doxorubicin [3]. The efficacy and toxicity of amrubicin is therefore largely dependent on the tissue distribution of amrubicinol. Among results to date, amrubicin showed more potent antitumor activity than doxorubicin in several human tumor xenografts implanted in nude mice [4], and antitumor activity was closely reflective of the tumor concentration of amrubicinol [5]. The acute toxicity profile of this agent is qualitatively comparable to that of doxorubicin [6], but it has rarely been shown to cause the delayed-type toxicity observed with doxorubicin, particularly cardiotoxicity [7, 8], nor did it exacerbate doxorubicin-induced myocardial toxicity in dogs [8]. Amrubicin and amrubicinol are weak DNA intercalaters and potent inhibitors of topoisomerase II [9].

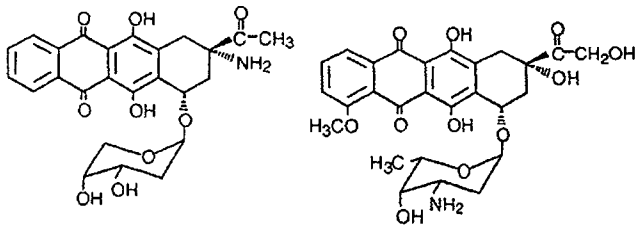

Fig. 1 Chemical structures of amrubicin and doxorubicin

Clinically, amrubicin showed substantial activity against NSCLC in an early phase II study of single intravenous injection of 120 mg/m^2 every 3 weeks, with a partial response (PR) rate in 5 of 20 previously untreated patients (25%; 95% CI, 8.7 to 49.1%) [10]. An additional phase I–II study for NSCLC was conducted by daily intravenous administration for three consecutive days [11], on the basis of experimental findings that amrubicin showed better efficacy in a divided treatment schedule than in a single injection [12]. The maximum tolerated dose was set at 50 mg/m^2/day and the recommended dose for the phase II study was 45 mg/m^2/day. Overall response rate in the phase I–II study was 25.0% (95% CI, 10.7 to 44.9%), with seven PRs in 28 previously untreated patients. These reproducible response rates of more than 20% in two clinical studies suggest that amrubicin may be a promising agent in the treatment of NSCLC, in contrast to doxorubicin which shows only marginal activity against NSCLC [13].

Here, we conducted one of two phase II studies with an identical protocol and monitoring to assess the efficacy and safety of amrubicin by daily intravenous administration for three consecutive days in previously untreated patients with advanced NSCLC.

Patients and methods

Eligibility

This study investigated patients with histologically or cytologically confirmed unresectable NSCLC in stages IIIA, IIIB, and IV. Eligibility criteria included no prior treatment, measurable lesions, an ECOG performance status of 0 to 2, an estimated life expectancy of at least 2 months, and age less than 75 years. Adequate organ function was also required, with a WBC count ≥4,000/μL, platelet count ≥100,000/μL, hemoglobin level ≥10 g/dL, AST and ALT< 100 U/L, total bilirubin level ≤1.5 mg/dL, serum creatinine level ≤1.2 mg/dL, ECG within normal limits, and left ventricular ejection fraction (LVEF, echocardiogram) ≥60%.

Exclusion criteria included symptomatic brain metastasis, bone metastasis requiring radiation treatment, accumulation of plural fluid requiring treatment like drainage, continuous long-term treatment with non-steroidal anti-inflammatory agents, glucocorticoids, or morphine derivatives, serious complications or other active cancer, and those judged by the investigators to be inappropriate for the study. Patients who were pregnant, breast-feeding, or taking inadequate contraceptive precautions were also ineligible. Further, the protocol was amended during the course of the study to exclude patients with confirmed or suspected interstitial pneumonitis owing to the exacerbation of asymptomatic interstitial pneumonitis, identified by chest X-ray or computed tomographic (CT) scan before treatment, in three patients in an identical study, of whom two died [14]. The study protocol was approved by the institutional review board at each hospital, and written informed consent was obtained from all patients prior to participation.

Treatment

Amrubicin (Sumitomo Pharmaceuticals Co., Ltd, Osaka, Japan) was supplied as a freeze-dried powder in vials containing 20 mg each. It was reconstituted in 20 mL of physiological saline or 5% glucose solution and given by intravenous infusion at 45 mg/m^2/day over 5 min on three consecutive days, with the cycle repeated every 3 weeks. A minimum of three cycles was undertaken except in the occurrence of disease progression, unacceptable toxicity or patient noncompliance.

Before treatment, all patients underwent medical history review, physical examination, hematology and serum biochemistry tests, urinalysis, electrocardiography (ECG), echocardiogram for left ventricular ejection fraction (LVEF), and baseline tumor measurements (e.g. chest radiography, CT scans, bone scintigraphy). Measurable and assessable lesions were evaluated within 2 weeks of the start of treatment, and ECG and LVEF within 1 month.

Laboratory variables were measured weekly as a rule, including complete differential blood cell counts, platelet counts, hematocrit, blood biochemistry, and urinalysis. Complete differential blood cell and platelet counts were obtained at least twice weekly when myelosuppression was observed. The ECG was measured with every treatment cycle, and the LVEF test every second cycle. Chest radiography and CT scans were carried out every cycle as a rule.

Subjective symptoms and objective signs were observed and recorded as required

Adjustment of dosage and schedule modification

Treatment was repeated when the WBC count recovered to ≥3,000/μL and the platelet count recovered to ≥100,000/μL. Treatment was delayed when recovery was incomplete until these values were reached, and withdrawn if they were not reached within 5 weeks. Dosage was maintained as in the previous course if the WBC nadir was <1,000/μL for ≤3 days, or ≥1,000/μL and the platelet nadir was ≥50,000/μL, and reduced by 5 mg/m^2/day from the previous dosage if the respective values were <1,000/μL for ≥4 days and/or <50,000/μL.

Response and toxicity evaluation

Response was assessed in accordance with the "Criteria for the evaluation of the clinical effects of solid cancer chemotherapy" of the Japan Society for Cancer Therapy [15], which are virtually identical to those of the World Health Organization [16], namely with a complete response (CR) defined as the disappearance of all lesions for a minimum of 4 weeks; a partial response (PR) as a 50% or greater decrease in the sum of the products of the diameters of the measurable lesions for a minimum period of 4 weeks and no new lesions; no change (NC) as a decrease in the tumor mass of less than 50% or any increase of less than 25%; and progression disease (PD) as an increase in the size of any measurable lesion by 25% or the appearance of new lesions.

Toxicity was graded based on the side effect record form of the Japan Society for Cancer Therapy criteria [15]. Toxicity items not included on the record form were recorded as present or absent without grading.

Table 1 Patient characteristics

Patient characteristics	No. of patients	Percent
No. of enrolled patients	62	
No. of eligible patients	60	
Age, years		
Median	65.5	
Range	41–75	
Gender		
Male	37	61.7
Female	23	38.3
Performance status (ECOG scale)		
0	8	13.3
1	41	68.3
2	11	18.3
Histology		
Squamous cell carcinoma	24	40.0
Adenocarcinoma	29	48.3
Large cell carcinoma	7	11.7
Stage		
IIIA	5	8.3
IIIB	14	23.3
IV	41	68.3

ECOG Eastern Cooperative Oncology Group

Table 2 Response to amrubicin

	No. of patients	Response (No. of patients)					Response rate, % [95%CI]
		CR	PR	NC	PD	NE	
Eligible patients	60	0	11	30	16	3	18.3 [9.5–30.4]
Histology:							
Squamous cell carcinoma	24	0	6	9	7	2	25.0
Adenocarcinoma	29	0	5	17	6	1	17.2
Large cell carcinoma	7	0	0	4	3	0	0
Stage							
IIIA	5	0	2	3	0	0	40.0
IIIB	14	0	3	7	3	1	21.4
IV	41	0	6	20	13	2	14.6
Performance status (ECOG):							
0	8	0	2	4	2	0	25.0
1	41	0	8	22	10	1	19.5
2	11	0	1	4	4	2	9.1

Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluated; ECOG, Eastern Cooperative Oncology Group

Statistical analyses

Primary endpoint was response rate. In this study, the number of patients was estimated as 60 to guarantee at least 10% response rate with a probability of 95% at 20% of expected response rate. Secondary endpoints were overall survival and safety. The time frame for overall survival was defined as the time from treatment until onset of the event. Kaplan–Meier life table was constructed for patient survival, 1-year survival, 2-year survival and median survival time [17]. All analyses were done using SAS, version 8.2 (SAS Institute Inc., Cary, North Carolina).

Results

Patient characteristics

Of 62 patients registered between April 1995 and September 1997 through 14 participating institutions in Japan, 60 patients were eligible and assessable for efficacy and 59 were assessable for safety (Table 1). Two patients were ineligible due to the protocol deviation in the inclusion criteria, not NSCLC in one patient and receiving prior chemotherapy in a second patient. Another patient was not safety-assessable due to a withdrawal of informed consent soon after the completion of first cycle treatment. By stage, 41 patients had stage IV disease, 14 had stage IIIB, and 5 had stage IIIA. Histologically, 29 patients had adenocarcinoma, 24 squamous cell carcinoma, and only 7 large cell carcinoma. Most patients had a good performance status (PS) of 0 or 1, but 11 (18.3%) had PS of 2. No patient had received any prior treatment, including radiotherapy.

Response and survival

Response among the 60 eligible patients was 11 PRs, giving an overall response rate of 18.3% (95% CI, 9.5 to 30.4%) (Table 2). Responders were 6 (25.0%) of 24 patients with squamous cell carcinoma and 5 (17.2%) of 29 with adenocarcinoma.

Regarding the overall survival curve, median survival time was 8.2 months (95% CI, 6.7 to 10.4 months), and 1- and 2-year survival rates were 34.9% and 7.6%, respectively (Fig. 2).

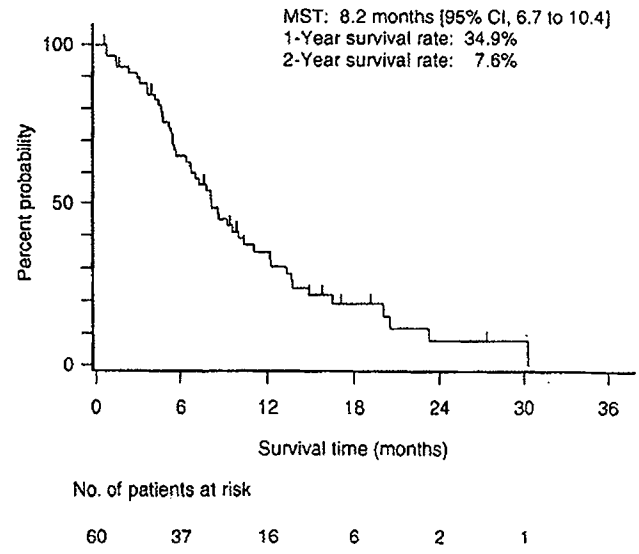

Fig. 2 Overall survival of patients with advanced non-small-cell lung cancer following treatment with amrubicin. Median survival time was 8.2 months (95% confidence interval, 6.7–10.4 months)

Table 3 Major treatment-related hematologic toxicity of amrubicin

Toxicity	No. of assessable patients	Toxicity grade					
		1	2	3	4	≥1	≥3
		(No. of patients)				Frequency (%)	
Anemia (hemoglobin)	59	16	17	16	2	86.4	30.5
Leukopenia	59	5	16	21	11	89.8	54.2
Neutropenia	59	0	7	12	34	89.8	78.0
Thrombocytopenia	59	12	3	9	8	54.2	28.8

Safety

Hematologic toxicities observed throughout the present clinical trial for which a causal relationship to amrubicin could not be denied are shown in Table 3. The most common was myelosuppression, particularly neutropenia, leukopenia and anemia (hemoglobin decrease) with frequencies of 89.8, 89.8 and 86.4%, respectively. Thrombocytopenia was somewhat lower frequent (54.2%). Among these, the incidence of grade 3 or 4 toxicity was 78.0% for neutropenia, 54.2% for leukopenia, 30.5% for anemia, and 28.8% for thrombocytopenia.

Although mild, non-hematologic toxicities included stomatitis, anorexia, nausea/vomiting, diarrhea, fever, alopecia, and AST/ALT elevation were each seen in more than 10% of the patients (Table 4). Grade 3/4 episodes were seen only for anorexia, nausea/vomiting, and alopecia with frequencies of each 1.7%. ECG abnormalities for which a relationship to amrubicin was unknown were seen in two patients, one with transient negative T and the second with ST depression, but were judged not to be clinically significant on review by a cardiologist. A decrease in LVEF for which a causal relation to amrubicin could not be denied was seen in two patients, one with a decrease from 73% at base line to 53% after three cycles of treatment and in the second from 69 to 52% after two cycles. LVEF values fluctuate readily under the influence of various factors, and these changes are not particularly abnormal. Moreover, no accompanying changes in ECG or symptoms were seen, and thus the medical significance was not clear. However, given that amrubicin is an anthracycline derivative, like doxorubicin, the cardiotoxicity of which is well known, treatment was discontinued as precaution.

Discussion

This present study indicates that amrubicin is an active agent in the treatment of patients with NSCLC. Overall response rate was 18.3% (95% CI, 9.5 to 30.4%) and median survival time was 8.2 months (95% CI, 6.7 to 10.4 months). In an identical study, which included 61 patients, amrubicin achieved overall response rate of 27.9%, with 1 CR and 16 PRs, and median survival was 9.8 months [14]. Thus, the overall response rate for amrubicin in these two studies with an identical protocol was 23.1% (95% CI, 16.0 to 31.7%).

Table 4 Major treatment-related non-hematologic toxicities of amrubicin

Toxicity	No. of assessable patients	Toxicity grade					
		1	2	3	4	≥1	≥3
		(No. of patients)				Frequency (%)	
Stomatitis	59	7	2	0	0	15.3	0
Anorexia	59	20	20	1	–[a]	69.5	1.7
Nausea and vomiting	59	21	11	1	–[a]	55.9	1.7
Diarrhea	59	9	0	0	0	15.3	0
Fever	59	8	7	0	–[a]	25.4	0
Phlebitis	59	2	0	0	0	3.4	0
Alopecia	58	27	16	1	–[a]	75.9	1.7
Total bilirubin elevation	58	4	0	0	0	6.9	0
AST elevation	59	10	1	0	0	18.6	0
ALT elevation	59	9	4	0	0	22.0	0
ALP elevation	59	3	1	0	0	6.8	0
BUN elevation	59	4	0	0	0	6.8	0
Others[b]	LVEF decrease, 2/42[c]; ECG abnormality, 2/54[c]						

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urine nitrogen; LVEF, left ventricular ejection fraction; ECG, electrocardiogram

[a] Toxicity grade not defined.

[b] Toxicities not graded.

[c] Ratio of number of reported patients to number of observed patients.

NSCLC is known to have poor sensitivity to chemotherapy [18–20], but the recent development of newer agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan has seen considerable improvements in therapeutic outcomes [21, 22], with response rates of more than 20% when used as single agents in previously untreated patients with advanced NSCLC. The present results indicate that amrubicin which is different from these newer agents in mode of action [9], namely the inhibition of topoisomerase II, is comparable to these newer agents in efficacy for NSCLC.

The major toxicity of amrubicin was hematologic, particularly neutropenia and leukopenia. In contrast, no febrile neutropenia was observed. Non-hematologic toxicity was relatively mild, with the only grade 3/4 episodes being seen for anorexia, nausea/vomiting, and alopecia with frequencies of each 1.7%. These safety results are supported by those from an identical study [14]. In that study, interstitial pneumonitis developed in three patients, of whom two died [14]. So the protocol was revised to exclude patients with confirmed or suspected interstitial pneumonitis. In the present study, interstitial pneumonitis was not seen.

Among cardiotoxicity, abnormalities in ECG and a decrease in LVEF were seen in two patients each. These changes were asymptomatic and did not overlap in the same patients. These findings suggest that unlike the case of cardiomyopathy caused by doxorubicin, the effect of amrubicin on cardiac function is neither serious nor definite. It is well known that doxorubicin experimentally and clinically causes cardiomyopathy which is cumulative toxicity caused by long-term treatment. In contrast, amrubicin on repeated administration did not cause cardiotoxicity or aggravate doxorubicin-induced cardiotoxicity in rabbits and dogs [7, 8]. Although cardiomyopathy has not been clinically observed to date, careful observation on the effects of amrubicin on the heart is required in further clinical studies, especially for patients on long-term treatment.

In conclusion, amrubicin showed promising activity against NSCLC in the present study. In a previous study, moreover, the combination of amrubicin and cisplatin demonstrated an impressive response rate and median survival time for extensive-stage SCLC (87.8% and 13.6 months, respectively) [23]. We are presently planning a phase II study of the combination of amrubicin and cisplatin for advanced NSCLC.

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