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Original Article

Daily Low-Dose Cisplatin and Concurrent Thoracic Irradiation for Poor-Risk Patients with Unresectable Non-Small-Cell Lung Cancer

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A pilot study was conducted to assess the efficacy and feasibility of daily low-dose cisplatin with concurrent thoracic irradiation for clinically unresectable non-small-cell lung cancer (NSCLC). Patients with inoperable NSCLC who had poor risk factors such as advanced age, poor performance status, poor lung function, or concomitant active malignancy were entered into the study. Low-dose cisplatin (6 mg/m^2) was administered daily before concurrent thoracic irradiation (2 Gy/day; total dose of 60 Gy) was given. Twenty-five patients were registered. The majority of the patients had either stage IIIA (24.0%) or stage IIIB (60.0%) disease. Fifteen patients (60.0%) completed the planned treatment. Both chemotherapy and radiotherapy were stopped in 3 patients (12.0%) due to poor response, and 7 patients (28.0%) partly received radiotherapy alone as a result of their toxicity response. The proportion of total administered dose to planned dose was 90.9% for chemotherapy and 99.3% for radiotherapy, which were comparable to those in previous studies for LA-NSCLC patients without poor risk factors. Grade 3 leukopenia and neutropenia developed in 14 patients (56.0%) and 10 patients (40.0%), respectively, but grade 4 toxicity was not encountered. Grade 3 pneumonitis and esophagitis were observed in 4 patients (16.0%) and 2 patients (8.0%), respectively. The overall response rate was 60.0%. The median survival time was 22 months, and the 2-year survival rate was 50.3%. Daily low-dose cisplatin and concurrent thoracic irradiation were well tolerated even by poor-risk patients with NSCLC, and showed a therapeutic efficacy similar to that for good-risk patients.

Key words: non-small-cell lung cancer, concurrent chemoradiotherapy, low-dose cisplatin, poor-risk factor

Lung cancer is the leading cause of cancer-related death in industrialized countries [1]. Surgery offers the best chance for the cure of early-stage non-small-cell lung cancer (NSCLC). However, only a minority of patients are diagnosed with operable disease, and approximately one-third of patients have unresectable locally advanced disease at the time of diagnosis. Although these patients have been previously treated with

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radiotherapy alone, the outcome has been poor (median survival time: MST 9.1 months, 2-year survival rate: 13.5%) [2]. Many groups have investigated combined chemoradiation approaches and reported favorable results compared with those of radiotherapy alone [3-5]. Furthermore, meta-analysis has demonstrated prolonged survival in patients with locally advanced NSCLC (LA-NSCLC) who received combined chemoradiotherapy in comparison with radiotherapy alone [6]. Recently, the West Japan Lung Cancer Group (WJLCG) and the Radiation Therapy Oncology Group (RTOG) reported that concurrent chemoradiotherapy yielded a significantly higher response rate and longer survival in patients with LA-NSCLC than did sequential administration of chemotherapy and radiotherapy [7, 8]. We previously reported that a combination of cisplatin (CDDP) and 5-fluorouracil with concurrent hyperfractionated thoracic irradiation was feasible and highly effective in the treatment of patients with LA-NSCLC [9]. Based on these results, chemoradiotherapy, particularly concurrent administration of chemotherapy and radiotherapy, is now frequently employed for the treatment of LA-NSCLC. In these previous trials, however, patients at an advanced age, with active concomitant malignancy, poor performance status (PS), or insufficient reserves of principal organ function were excluded, because they were considered to be incapable of tolerating intensive treatment such as concurrent chemoradiotherapy or CDDP-based combination chemotherapy. Accordingly, these poor risk patients are generally treated with radiotherapy or supportive care alone, though the outcome is considered to be poor. We suspected that the treatment outcome of poor risk patients could be improved by combining low-dose chemotherapy with radiotherapy. It is well known that CDDP has a radiosensitizing potential [10]. Although the feasibility of combined modality treatment consisting of low-dose CDDP and thoracic radiotherapy for good-risk patients has already been established by several previous studies, its effectiveness has not been fully confirmed [11-15]. Schaake-Koning reported the survival advantage of a combination of daily low-dose CDDP and concurrent radiotherapy over that of radiotherapy alone in patients with LA-NSCLC [12]. However, Trovo obtained contradictory results [13]. Therefore, we planned a pilot study of a combined modality treatment consisting of daily low-dose CDDP and concurrent thoracic radiotherapy for patients with NSCLC having various poor risk factors. The objectives of this study were to confirm the feasibility of this combined modality treatment in poor-risk patients and to evaluate its effectiveness for LA-NSCLC.

Materials and Methods

Eligibility. Patient eligibility criteria included at least one of the following poor prognostic factors: advanced age (> 75 years), PS 3 on the Eastern Cooperative Oncology Group (ECOG) scale [16], active concomitant malignancy, and poor pulmonary function (PaO_2 < 60 Toll). The other eligibility requirements for entry into this study were as follows: 1) histologically or cytologically proven NSCLC; 2) bidimensionally measurable disease; 3) adequate function of the kidneys (creatinine clearance > 60 ml/min), liver (ALT and AST < twice the upper limit of normal), and bone marrow (leukocyte count > 3,500/μl and platelet count > 100,000/μl); and 4) acquisition subsequent to obtaining informed consent.

Although patients with distant metastasis, pleural effusion, or pericardial effusion were excluded from this study, those with local recurrence after surgical resection were included.

Evaluation. Staging procedures included a complete medical history and physical examination, urinalysis, complete blood cell count (CBC), standard biochemistry profile, 24-hour creatinine clearance (CCr), electrocardiogram, chest radiography, fiberoptic bronchoscopy, computerized tomography (CT) scans of the chest and abdomen, magnetic resonance imaging of the brain, and radionuclide bone scintigraphy. CBC was repeated twice a week, and urinalysis, biochemistry tests, 24-hour CCr, and chest radiography were performed at least once a week after the initial evaluation. CT scans of the chest were repeated once per treatment cycle. After the completion of chemoradiotherapy, each patient was re-staged with all of the tests used for the initial evaluation. The progression-free survival time and overall survival time were calculated from the date of initiation of therapy by using the Kaplan-Meier method. Response and toxicity were evaluated according to the WHO criteria [17]. Grading of pulmonary and esophageal toxicity caused by radiotherapy was performed according to the EORTC/RTOG criteria [18]. Statistical analysis was performed using the SPSS Base System™ and Advanced Statistics™ programs (SPSS Inc, Chicago, IL, USA).

Treatment. CDDP (6 mg/m^2 in 500 ml of physiological saline) was given as a 1-hour intravenous infusion

at 2 h before irradiation. Radiotherapy at a total dose of 60 Gy (2 Gy/fraction/day) was delivered through 2 opposing anterior-posterior fields using a linear accelerator, with the initial irradiation totaling 40 Gy and the boost irradiation totalling 20 Gy. The initial volume included the primary tumor, ipsilateral hilum, and whole width of the mediastinum with a margin of 2 cm around the radiographically visible involvement. The supraclavicular region was also included if involved. The boost volume included the primary tumor and all involved lymph nodes, the involvement of which was determined by CT scan.

Results

Patient characteristics. Between October 1994 and September 2000, 25 patients were entered into this study and fully evaluated. Subjects included 21 men and 4 women with a median age of 71 years (56–80). PS was 0 in 6 patients, 1 in 16, 2 in 1, and 3 in 2. Twelve patients had adenocarcinoma, 9 had squamous cell carcinoma, 1 had large cell carcinoma, and 3 had other cancers. Clinical stage was IB in 3 patients and IIA in 1. The majority of the patients had stage IIIA (24.0%) or stage IIIB (60.0%) disease. Poor risk factors, which were the basis for enrollment in this study, are listed in Table 1. All patients had at least one poor risk factor. Seven patients (28.0%) had respiratory dysfunction (PaO_2 $<$60 Toll) and seven had active concomitant malignancies, which included renal cell carcinoma in 3 patients, and hepatocellular carcinoma, ureteral carcinoma, and laryngeal carcinoma, respectively, in the 3 remaining patients. Six patients (24.0%) were elderly ($>$75 years old).

Treatment delivery. Fifteen patients (60.0%) completed the planned treatment. In 3 patients (12.0%), chemoradiotherapy was stopped at radiation doses of 50 Gy, 46 Gy, and 42 Gy, respectively, due to poor response (2 for NC and 1 for PD). Chemotherapy was stopped in 7 patients. In 4 patients, due to myelosuppression at radiation doses of 54 Gy, 54 Gy, 50 Gy, and 48 Gy, respectively, due to mild decline of renal function in 2 patients at 50 Gy and 16 Gy, respectively, and due to esophagitis in 1 patient at 42 Gy. Due to the aforementioned toxicities, 7 patients (28.0%) only received a portion of the radiotherapy. In the remaining 8 patients, treatment was interrupted and postponed as a result of toxicity, including neutropenia in 3 patients, obstructive pneumonia in 2, and emesis, esophagitis, and the physician's discretion, respectively, in the remaining 3. In the present study, the initially planned dose was 6 mg/m^2 $\times$ 30 (total 180 mg/m^2) for chemotherapy and 60 Gy for radiotherapy. The proportion of total administered dose to planned dose, which was calculated as the mean of actually administered dose/planned dose in each patient, was 90.9% for chemotherapy and 99.3% for radiotherapy.

Toxicity. The toxicities observed in this study are listed in Table 2. No treatment-related death occurred. Myelosuppression was the principal toxicity. Grade 3 leukopenia and neutropenia were observed in 14 patients (56.0%) and 10 patients (40.0%), respectively, though severe myelosuppression (grade 4 toxicity), neutropenic fever, and bleeding episodes were not encountered. Only 4 patients received granulocyte-colony stimulating factor

Table 1 Poor-risk factors in 25 patients

Poor-Risk Factors	No. (%) of patients
Respiratory dysfunction	7 (28.0)
Active concomitant malignancy	7 (28.0)
Advanced age (≧ 76 years old)	6 (24.0)
Local recurrence after surgery	4 (16.0)
Poor performance status (≧ 2)	3 (12.0)
Severe cardiovascular disease	2 (8.0)

Each patient had at least one poor-risk factor. Two patients had 2 poor-risk factors and 1 patient did 3.

Table 2 Toxicity

	Grade				
	0	1	2	3	4
Hematological toxicity					
Leukopenia	2	0	9	14	0
Neutropenia	2	4	9	10	0
Thrombocytopenia	3	13	7	2	0
Anemia	2	9	11	3	0
Non-hematological toxicity					
Esophagitis	14	8	1	2	0
Pneumonitis	19	2	0	4	0
Dermatitis	22	1	0	0	0
Nausea/vomiting	12	8	2	3	0
Renal dysfunction	24	1	0	0	0

G-CSF was administered to 4 patients (16%) with a median duration of 6 days (range, 4–14 days).

during neutropenia. With regard to non-hematological toxicity, grade 3 pneumonitis and esophagitis were observed in 4 patients (16.0%) and 2 patients (8.0%), respectively, but no life-threatening complications occurred.

Response and survival. Among 25 evaluable patients, one patient (4.0%) achieved complete response and 14 (56.0%) showed partial response. Thus, the overall response rate was 60.0%, with a 95% confidence interval of 40.8–79.2%. There were 8 patients (32.0%) with no change (NC) and 2 patients (8.0%) with progressive disease (PD).

At a median follow-up time of 37 months (4–77 months), 16 of the 23 patients had recurrence. Fig. 1 shows the time to progression. The median progression-free survival time was 10.0 months, and at 1, 2, and 3 years after treatment, 48.0%, 24.4%, and 24.4%, respectively, of the patients were free from progression. The initial sites of failure are listed in Table 3. Initial failure occurred in distant organs, including the lung, brain, bone, and skin, more frequently than at the local site. Malignant pleural effusion or pericardial effusion were also frequently observed. Overall survival is shown in Fig. 2. The MST was 22 months, and the 1-, 2-, 3-, and 4-year survival rates were 74.7%, 50.3%, 35.2%, and 15.6%, respectively. According to clinical stage, 3 patients with stage I disease died. One died of concomitant hepatocellular carcinoma after 55 months, and another died of pneumonia after 12 months. Only one patient died, after 25 months, of this LA-NSCLC. The patient with stage II disease was still alive without progression at the time of this report. For stage IIIA and IIIB patients, the MST was 41 and 14 months, and the 2-year survival rates were 83.3% and 20.0%, respectively.

Discussion

It is well recognized that combined chemoradiotherapy plays an important role in the treatment of unresectable LA-NSCLC [3–6]. In 2 recent large-scale phase III trials, the concurrent administration of intensive chemotherapy and thoracic irradiation was shown to have a survival advantage over sequential administration [7, 8]. However, severe toxicities are inevitable with such intensive combined modality treatment. Myelosuppression and esophagitis seem to be the major obstacles to concurrent chemoradiotherapy [7, 8]. Therefore, it is considered that the concurrent administration of intensive chemotherapy and thoracic irradiation is intolerable in poor-risk patients. On the other hand, previous studies have shown that concurrent administration of daily low-dose CDDP

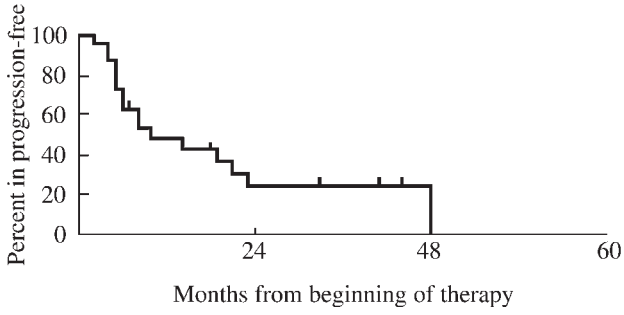

Fig. 1 Kaplan-Meier plot of progression-free survival: The median progression-free survival time was 10.0 months, and at 1, 2, and, 3 years after treatment, 48.0%, 24.4%, and 24.4% of the patients, respectively, were free from progression.

Table 3 Pattern of initial failure

	No. (%) of patients
No. of patients evaluated	25 (100.0)
No. of patients failed	16 (64.0)
Local progression only	5 (20.0)
Distant progression only	7 (28.0)
Lung metastasis*	3 (12.0)
Brain metastasis*	2 (8.0)
Bone metastasis	2 (8.0)
Subcutaneous metastasis	1 (4.0)
Malignant pleural effusion	3 (12.0)
Malignant pericardial effusion	2 (8.0)

*One patient developed metastases at lung and brain concomitantly

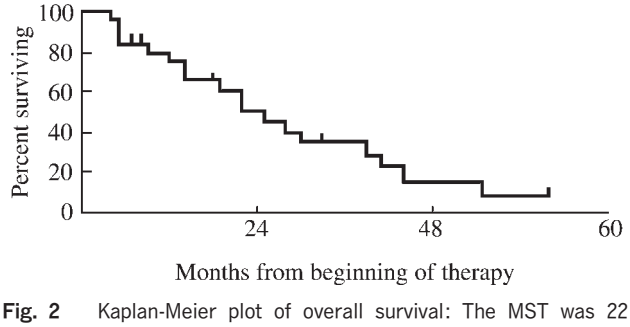

Fig. 2 Kaplan-Meier plot of overall survival: The MST was 22 months, and the 1-, 2-, 3-, and 4-year survival rates were 74.7%, 50.3%, 35.2%, and 15.6%, respectively.

and thoracic irradiation is less toxic, and feasible [11–15]. However, these studies excluded LA-NSCLC patients with poor risk factors such as poor PS, advanced age, insufficient functional reserves of the principal organs, or active concomitant malignancy. Accordingly, the feasibility of such combined therapy in poor-risk patients had not been confirmed previous to this study. We here demonstrated that this chemoradiotherapy was well tolerated, even by patients having various poor risk factors. Neither treatment-related mortality nor grade 4 toxicity was experienced. In the present study, 3 patients (12.0%) did not complete the planned radiotherapy as a result of poor response, and 7 patients (28.0%) could not complete the chemotherapy as a result of toxicity. However, the proportion of total administered dose to planned dose was 90.9% for chemotherapy and 99.3% for radiotherapy, which is comparable to the ratio reported in previous studies [9, 14]. The major toxicities of this chemoradiotherapy were leukopenia and neutropenia, but these problems were not severe. Administration of G-CSF was required in only 4 (16.0%) patients, and no patient received platelet transfusion. Radiation-induced esophagitis and pneumonitis are often the principal toxicities interrupting concurrent chemoradiotherapy. Although recent trials of chemoradiotherapy with paclitaxel or docetaxel have shown hopeful results, the incidence of esophagitis and pneumonitis was quite high [19, 20]. In the present study, grade 3 or 4 radiation esophagitis occurred in only 2 patients (8.0%), and interruption of therapy due to radiation esophagitis was required in only 1 patient. In the patients who completed the planned chemoradiotherapy, toxicity was particularly mild, and no patient experienced grade 3 radiation esophagitis. These results are considered to be superior to those in previous reports of chemoradiotherapy for LA-NSCLC patients without poor risk factors [12, 14]. Grade 3 radiation pneumonitis occurred in four patients (16.0%), which incidence is high compared with those in previous reports [11–15], but no life-threatening pneumonitis was experienced. (Among the 4 patients developing grade 3 radiation pneumonitis, 2 had poor lung function before treatment, which might have been the reason behind the high incidence of pulmonary toxicity.) We also confirmed that this regimen was reasonably effective for LA-NSCLC. Previously, Shaak-Koning and Jeremic reported a survival benefit of simultaneous daily administration of CDDP or carboplatin plus thoracic irradiation in comparison with irradiation alone, which was mainly due to improved local control [12, 21]. On the other hand, Trovo reported contradictory results [13], though the total dose of radiation in their trial (45 Gy) was less than the optimal dose. Thus, the effectiveness of radiosensitization by CDDP or carboplatin in patients with LA-NSCLC has not yet been established. Furthermore, in Shaake-Koning's study, 2 separate treatment periods, with a 4-week pause between the first course (30 Gy) and the second course (20 Gy) of therapy, were adopted to reduce the toxicity [12]. Generally, a split schedule of radiotherapy is considered to be suboptimal because repopulation of tumor cells occurs during the rest period. Therefore, we planned to employ a combination of continuous daily thoracic radiotherapy and low-dose CDDP. Our regimen achieved an overall response rate of 60.0%, which is similar to that for other chemoradiotherapy trials. Only 5 patients (20.0%) had experienced local failure at the time of this report, which indicates quite good local control compared to the results of intensive concurrent chemoradiotherapy reported by the WJLCG (32.7%) and RTOG (33%) [7, 8]. Despite the limited number of patients assessed in this study, the overall survival of stage IIIA and IIIB patients appears to be superior to that obtained previously with intensive chemoradiotherapy regimens.

In conclusion, we confirmed that the combination of low-dose daily CDDP plus concurrent thoracic irradiation is well tolerated and can achieve encouraging results even in poor-risk patients with NSCLC. These results warrant further studies to confirm the efficacy of this combined modality treatment for patients with LA-NSCLC.

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