Phase II Trial of Daily Low-dose Carboplatin and Thoracic Radiotherapy in Elderly Patients with Locally Advanced Non-small Cell Lung Cancer

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Background: The purpose of this study was to investigate the feasibility of concurrent thoracic radiotherapy (TRT) and daily low-dose carboplatin (CBDCA) in elderly patients with locally advanced non-small cell lung cancer (NSCLC) and to estimate tumor response, toxicity and survival.

Methods: Forty patients were entered in a multicenter phase II study. All were patients with pathologically documented unresectable stage IIIA or IIIB or medically inoperable stage I, II NSCLC. CBDCA 30 mg/m² was given on days 1–5 in weeks 1–4 concurrently with TRT, mainly for radiosensitization. TRT was started 1 h after CBDCA (30 min infusion) was given. TRT was given in 2 Gy/fraction/day, 5 days a week for a total of 50–60 Gy.

Results: Thirty-eight patients were assessable for treatment response and toxicity. One patient had a CR and 18 patients PRs with a response rate of 50% (95% CI, 33.4–66.6%). The main toxicities were hematological toxicity. Other toxicities were grade ≥2 esophagitis in one patient, grade 3 nausea/vomiting in one and grade ≥3 pulmonary toxicity in two. There was one treatment-related death due to pulmonary toxicity. For stage IIIA + IIIB patients, the median survival time was 15.1 months and 1- and 2-year actuarial survival rates were 52.6 and 20.5%, respectively. For stage I + II patients, 1- and 3-year actuarial survival rates were 90.9 and 69.3%, respectively.

Conclusions: The data suggest that TRT with daily low-dose CBDCA in elderly patients is effective and feasible because of its low toxicity and survival.

Key words: non-small cell lung cancer – elderly patients – carboplatin – radiosensitizer – chemoradiotherapy

INTRODUCTION

In Japan, it is expected that the population of the elderly will increase still further in the future. In 1996, the proportion of Japanese population older than 65 years had increased to 15% and the number of people older than 65 years exceeded 19 million (1). Moreover, the risk of cancer grows as age advances. Lung cancer is the leading cause of cancer-related death and mortality rates for lung cancer have been increasing continuously among the elderly. Lung cancer death rates for men and women aged ≥75 years have now peaked at approximately 240–310 per 100 000 population (1). The management of lung cancer in the elderly poses various problems in Japan. Generally, old age is accompanied by decreasing organ function, an increase in complications and changes in the perception of both quality of life and life expectancy. Surgery offers the best chance for cure in stage I and II non-small cell lung cancer (NSCLC). Unfortunately, only a small minority of patients are diagnosed with operable early stage disease. Furthermore, there is a clear difference in aggressive treatment rate for NSCLC between elderly patients and younger patients. The elderly patients are less likely to receive more aggressive treatment such as surgery or chemotherapy (2). For many years, the standard treatment for locally advanced NSCLC has been thoracic radiotherapy (TRT), although long-term survivors are rare. The 5-year survival rate of patients with stage III NSCLC is <10% (3–5). Many randomized clinical
trials have been undertaken to investigate whether survival time improved for patients with locally advanced NSCLC who received chemo-radiotherapy combinations compared with TRT alone (6–12).

Recently, meta-analysis has indicated that chemotherapy plus RT showed a survival advantage compared with RT alone (13,14). The European Organization for Research and Treatment of Cancer (EORTC) conducted a randomized three-arm trial that compared split-course RT alone to 55 Gy with the same RT plus concurrent cisplatin (DDP) given daily (6 mg/m²) or weekly (30 mg/m²) (11). Survival was significantly better in the daily DDP with TRT group than in the TRT group ($p = 0.009$), while survival in the weekly DDP with TRT group was not significantly different from that of the other two groups. Carboplatin (CBDCA), an analogue of cisplatin, shows no nephrotoxicity, neurotoxicity or ototoxicity and is much less emesis-provoking than cisplatin (15–17).

The radiosensitizing properties of CBDCA have been shown in experimental investigations (18–21). Therefore, we considered CBDCA to be more acceptable in the treatment of elderly patients.

Based on these considerations, we conducted a phase II study of daily low-dose CBDCA and TRT in patients aged ≥76 years with unresectable locally advanced or medically inoperable stage I or II NSCLC.

### MATERIAL AND METHODS

#### PATIENT ELIGIBILITY

The criteria for entry to the study were as follows: a histologically confirmed non-small cell carcinoma; medically inoperable or unresectable stage I, II, IIIA, IIIB; no previous therapy; age ≥76 years; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; no evidence of distant metastases; white blood cell (WBC) count ≥3000/µl; hemoglobin level ≥9.5g/dl; platelet (Plt) count ≥100 000/µl; serum bilirubin level <1.5mg/dl; serum AST/ALT < twice the upper limit of normal; renal function (serum creatinine and blood urea nitrogen; urinalysis, and chest-X rays were evaluated in accordance with the World Health Organization (WHO) criteria (23), but grading of esophageal toxicity due to radiation was defined according to ECOG criteria.

#### TREATMENT

Radiotherapy and chemotherapy were undertaken concurrently (Fig. 1). Chemotherapy was given as follows: patients received CBDCA 30 mg/m² intravenously (30 min infusion) on days 1–5 in weeks 1–4 concurrently before TRT, mainly for radiosensitization. Patients received 100 ml of normal saline with CBDCA. A single dose fraction of 2 Gy was administered daily in five fractions per week. The initial dose of 40 Gy was administered to an area including the primary tumor, along with the ipsilateral hilar and mediastinal lymph nodes, with at least 2 and 1 cm margins around the contralateral non-involved hilar and mediastinal lymph nodes, respectively. The supraclavicular lymph nodes were included in the treatment field if metastases were clinically evident. Supraclavicular nodes were included when the primary tumor was located in the upper lobe or when a superior mediastinal mass was present. The lower margin of the treatment portal was at least 3 cm below the carina, except in patients with middle- or lower-lobe primary tumors, in which case the entire lower mediastinum was irradiated. An additional 10–20 Gy were administered to a reduced field consisting of the primary tumor and involved lymph nodes. The spinal cord was excluded from the irradiated volume at 40 Gy by use of a parallel, opposed oblique field. Patients were treated with megavoltage photons (10 MeV photons). If the patient presented with stage I NSCLC, the radiation field principally included only the primary tumor site itself. In the case of stage II, the radiation portals included the ipsilateral hilum alone. If the WBC count was <2000/µl or the platelet count was <50 000/µl during combined treatment, CBDCA and radiation therapy were discontinued until recovery of WBC to a level of ≥2000/µl and platelets to ≥50 000/µl. If grade 4 myelotoxicity developed during radiation alone, TRT was discontinued until recovery to grade <3.

If grade 3 or 4 toxicity radiation-induced esophagitis occurred, according to ECOG criteria (22), radiotherapy was withheld until esophagitis recovered to grade 1 or 2. If the PaO₂ decreased by ≥10 Torr, TRT was withheld until PaO₂ recovered. If the body temperature was greater than >38°C, TRT was withheld until it recovered to normal levels.

#### EVALUATION

For assessment of response and toxicity, all patients received a complete blood cell count, blood chemistries, including AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin, creatinine and blood urea nitrogen; urinalysis, and chest-X rays once weekly during the treatment period. Response and toxicity were evaluated in accordance with the World Health Organization (WHO) criteria (23), but grading of esophageal toxicity due to radiation was defined according to ECOG criteria.

### Table

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 22</th>
<th>Day 29</th>
<th>Day 36</th>
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</tr>
<tr>
<td>CBDCA</td>
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<td>++++</td>
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</tr>
</tbody>
</table>

**Figure 1.** Treatment scheme of concurrent chemo-radiation therapy in the elderly.
The eligibility, assessability and response of each patient were assessed by independent reviewers. A complete response (CR) was defined as the disappearance of all measurable lesions for at least 4 weeks. A partial response (PR) was defined as a ≥50% decrease in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks without the development of new lesions. If no response or progression of disease occurred during treatment, patients were considered to have stable disease. PD was defined as a ≥25% increase in the sum of the products of the perpendicular diameters of all measurable disease or the appearance of new lesions.

STATISTICAL ANALYSIS

This study was designed to detect a response rate (CRs plus PRs) of 70% compared with a minimal, clinically meaningful response rate of 50%. Employing $\chi^2 = 0.05$ and $\beta = 0.20$, the target number of cases required to be detected would be 37 (24). Assuming the loss of follow-up cases to be 5%, 40 patients would be entered in this study. Survival was calculated according to the period from the start of treatment to death or last follow-up evaluation. The survival curve was calculated using the method of Kaplan and Meier (25). Analysis was based on all eligible patients unless stated otherwise. Exact tests were used to compare response rate and toxicity.

RESULTS

Forty patients were entered into the study between November 1993 and July 1997. Of these, two patients were ineligible, one because of age <75 years and the other because of mental deterioration. Thus, 38 patients were eligible and assessable for response, survival and toxicity analysis. The characteristics of the 38 patients are listed in Table 1. Their ages ranged from 76 to 84 years, with a median of 79 years.

There were 30 men and eight women. Twelve patients had stage I or II disease. Half of the cases had stage IIIA. Adenocarcinoma occurred more frequently [22 (57.9%)] than squamous cell carcinoma [15 (39.5%)] and large-cell carcinoma [1 (2.6%)].

The reasons for refraining from surgery in 12 patients with stage I and II were as follows: two patients refused to be operated upon, seven were considered to be inoperable, owing to poor pulmonary function or poor general condition, and three were judged stage I or II from stage IIIA by extramural reviewers.

RESPONSE

The responses to combined treatment are listed in Table 2. Of 38 patients assessable for response, one (2.6%) achieved a CR and 18 (47.4%) achieved a PR with an overall response rate of 50% [95% confidence interval (CI) 33.4–66.6%], whereas 19 (50.0%) had no change and none indicated progression. Patients with stage I and II tended to respond poorly compared with those with stage IIIA and IIIB (response rate 33.3 vs 57.7%). The response rate of 57.7% in patients with stage IIIA and IIIB was higher than the response rate of 33.3% in patients with stage I and II, but it was not a significant difference ($p = 0.15$, Fisher’s exact test).

The response rates for squamous and non-squamous cell carcinoma were 73.3% (11/15) and 34.8% (8/23), respectively. There was no significant difference ($p = 0.40$) between the response rate for squamous and non-squamous cell carcinoma.

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
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<tr>
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<tr>
<td>2</td>
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<tr>
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<td>T2</td>
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<td>8</td>
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<td>6</td>
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<tr>
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</table>

TOXICITY OF TREATMENT

Hematological and non-hematological toxicity were analyzed during treatment and the follow-up period. Table 3 summarizes the hematological toxicity. Grade 3 or 4 leukopenia was
Chemo-radiotherapy in elderly patients with NSCLC

observed in 71.1% of the patients (66.6% in stage I and II, 73.1% in stage IIIA and IIIB) and 55.3% of the patients experienced grade ≥3 neutropenia (58.3% in stage I and II, 53.8% in stage IIIA and IIIB). Eleven patients (28.9%) experienced grade ≥3 thrombocytopenia (33.3% in stage I and II, 26.9% in stage IIIA and IIIB). Grade ≥3 anemia was noted in 13 patients (34.2%) (8.3% in stage I and II, 46.2% in stage IIIA and IIIB, \( p = 0.02 \)).

Non-hematological toxicity was relatively mild (Table 4). None of the patients developed grade ≥3 esophagitis. Other toxicities were grade 3 nausea/vomiting in one and grade 4 pulmonary toxicity in two patients. These two patients with grade 4 pulmonary toxicity died of pneumonitis at 5 weeks and 4 months after therapy, respectively. One patient had stage IIIA (T3N2) squamous cell carcinoma and the other had stage IIIB (T4N2) squamous cell carcinoma. These patient’s deaths were considered to be treatment-related.

**CARBOPLATIN AND RADIATION DOSE ADMINISTERED**

The actual doses of CBDCA and RT administered are presented in Table 5. None of the patients were taken off treatment due to progressive disease. It was possible to give CBDCA in almost all cases according to the plan. One patient received only four doses of CBDCA owing to deterioration of cardiac function. Thirty-four patients (89.5%) completed RT as planned while four (10.5%) did not complete it.

**SURVIVAL**

The median follow-up time was 27.6 months (range, 6.3–53.1 months). Twenty-two (57.9%) patients had died at the time of analysis. Causes of death included progression of lung cancer in 19 patients (86.4%), bacterial pneumonia in one (4.5%) and pneumonitis in two (9.1%). Sixteen patients remain alive, nine with stage I and II and seven with stage IIIA and IIIB. For stage IIIA and IIIB patients, the median survival time was 15.1 months and 1- and 2-year actuarial survival rates were 52.6 and 20.5%, respectively (Fig. 2). For patients with stage I and II, 1- and 3-year actuarial survival rates were 90.9 and 69.3%, respectively. The median survival time had not yet been reached for stage I and II patients at the time of analysis. The median survival time for all patients was 18.8 months.

**PATTERN OF FAILURE**

The first sites of relapse were investigated in 19 responders. Fifteen patients had local relapse and/or distant metastases and four had no relapse at the time of analysis. The primary tumor site was the first site of relapse in 10 patients (66.7%). Distant metastasis was the first site of relapse in five patients (33.3%) (brain in three, bone in two).

**DISCUSSION**

In general, elderly patients ≥75 years old are excluded from clinical studies and aggressive treatment in clinical practice. So
far, there have been few studies that have reported the treatment of elderly patients with NSCLC. This may be for various reasons, such as poor tolerance of toxicity, stress of treatment, co-morbidity and issues of mental status. Consequently, there is little information on cancer treatment in this age group. Radiotherapy is an effective treatment modality for lung cancer. In order to improve the clinical outcome, one strategy combines chemo-radiotherapy in patients with stage III NSCLC. However, the best regimen and schedule to combine with RT is still unclear. One approach is the use of standard dose chemotherapy in combination with TRT, concurrently or sequentially. The findings of a study by Furuse et al. (26) suggested that concurrent chemo-radiotherapy results in a better response and survival than chemotherapy followed by irradiation. Another approach is to use drugs as a radiosensitizers with TRT on a weekly or daily basis. The latter strategy seems to be suitable for elderly or frail patients.

In this study, we examined the feasibility and efficacy of this regimen in locally advanced NSCLC patients aged ≥76 years. The response rate for all patients was 50%, which is not considered as effective as previous combined treatment trials. The unsatisfactory local control rate may be due to the low dosing of CBDCA and/or insufficiency of radiation dose (<60 Gy).

Alternatively, it could be that the schedule, dose of CBDCA or the timing of RT and CBDCA injection were not optimal. Kunito et al. (27) reported a phase II trial using accelerated hyperfractionated (HF) TRT (total 60 Gy), combined with daily CBDCA, in locally advanced NSCLC. That study included very poor risk and/or aged patients, with a median age of 73 years. CBDCA at 25 mg/m² i.v. was given on each day of TRT and the total dose of CBDCA was 500 mg/m² over the 4 weeks. Jeremic et al. (8) reported a randomized study using HF TRT (69.6 Gy) versus HF TRT and concurrent CBDCA and VP-16 in stage III NSCLC within an age range of 42–67 years. In that study, chemotherapy consisting of 50 mg of CBDCA and 50 mg of VP-16 was given on each RT day. As a way to improve the response rate and survival, combination chemotherapy may be preferred to a single agent. However, in the treatment of cancer in older people, this is not always appropriate because of reduced life expectancy and treatment tolerability. It is equally important to estimate symptom control, quality of life and the safety level of cancer treatment in elderly patients. Aggressive cytotoxic combination chemotherapy with TRT in elderly patients may be associated with severe and unpredictable adverse effects. As mentioned above, there are positive trials of combined modality treatment that had the eligibility criteria excluding the elderly patients (age >70 years) (10,11). At the moment, it seems unclear whether aggressive treatment is suitable for the elderly patients or not.

In elderly patients, it seemed reasonable to combine the daily low-dose anti-cancer drug for radiosensitizing properties with TRT rather than combination standard dose chemotherapy. Although we observed a relatively disappointing objective response rate of 50%, the median survival time of 15.1 months and 1-year survival rate of 52.6% are encouraging for the stage III and IIIB patients. Furthermore, for the stage I and II patients, 1- and 3-year actuarial survival rates were 90.9 and 69.3%, respectively. Noorjik et al. (28) reported a study of radiotherapy with curative intent for 50 patients with peripherally located NSCLC. The survival rates were 56% at 2 years and 16% at 5 years with a median survival of 27 months. Furuta et al. (29) reported that the 2- and 5-year overall survival rates were 40 and 16% for patients aged ≥75 years with stage I and II NSCLC who were given definitive radiotherapy. Our data are not inferior to these results. Sibley (30) reported a review of radiotherapy for patients with medically inoperable stage I non-small cell lung carcinoma. There are 10 retrospective studies of medically inoperable stage I lung cancer. The 5-year overall survival rate in most series is approximately 15%. Age <70 years was reported to be a significant prognostic factor.

The survival advantage in this phase II trial should be investigated further to ascertain whether this treatment is better than radiotherapy alone in improving the survival of elderly patients with locally advanced NSCLC. In conclusion, our data suggest that TRT with daily low-dose CBDCA in elderly patients is suitable because of its low toxicity and enhanced survival. Therefore, a randomized trial of TRT alone vs TRT + daily low-dose CBDCA in elderly patients with locally advanced NSCLC should be conducted in the future.

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