COMBINED CHEMORADIOThERAPY WITH DAILY LOW-DOSE CISPLATIN IN STAGE III NON-SMALL CELL LUNG CANCER—AN INTERIM REPORT—

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Abstract: Purpose: To improve the local control of stage III non-small cell lung cancer, we tried concurrent chemoradiotherapy with daily low-dose cisplatin during the first 5 weeks of conventional radiotherapy.

Material and Methods: Ten consecutive patients with stage III non-small cell lung cancer were treated with chemoradiotherapy with 66 Gy in conventional fractionation and concurrent daily low-dose cisplatin (4 mg/m²), which was given 5 days per week (from Monday to Friday) for the first 5 weeks.

Results: There was no case with grade 3 toxicity. The median survival was 14.6 months, and the 2-year local progression-free survival rate was 35%.

Conclusion: Daily low-dose cisplatin combined with conventional radiotherapy was considered to be feasible and to have the possibility to offer better local control than radiotherapy alone in the treatment of stage III non-small cell lung cancer.

Key words: Non-small cell lung cancer, Combined modality therapy, Radiation therapy, Cisplatin

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common malignant tumor in Japan and accounts for 75-80% of all lung cancer. Despite recent advances both in radiotherapy and chemotherapy the prognosis of patients with inoperable stage III NSCLC remains poor. Frequent distant metastases and poor local tumor control are listed as the two main reasons for the poor prognosis. Local tumor control in patients with stage III NSCLC by conventional radiotherapy with 60 Gy is achieved in only about 15% to 17% of cases at 1 year. In addition to its necessity for cure, local control of disease is important for quality of life as well. Therefore, strategies for improving local tumor control are considered to be more important than the use of chemotherapy to suppress distant metastases.

Several strategies have been investigated to improve local disease control. One approach uses anticancer agents in conjunction with radiotherapy, and several of these approaches appear to be effective.

Anticancer drugs may be given before radiation (known as neoadjuvant chemotherapy), concurrent with radiation, and/or after radiation therapy is completed (adjuvant chemotherapy). The EORTC study has demonstrated in a randomized trial that daily cisplatin and radiation significantly improve both survival and local control rates compared with radiation alone. The authors suggested the radiosensitizing effect of daily cisplatin as a contribution to survival and local control rate improvement. The results of this study prompted us to investigate concurrent chemoradiotherapy for stage III NSCLC.

In our study, we modified the EORTC schedule of concurrent chemoradiotherapy in order to avoid cancer cell repopulation during treatment and also to reduce toxicity. The rest period of 3 weeks in the middle of 4 treatment weeks in the EORTC study was omitted and the patients were treated with a single uninterrupted course of 66 Gy. To reduce toxicity we used conventional fractions of 2 Gy rather than 3 Gy and 2.5 Gy in the EORTC study. We also reduced daily cisplatin dose to 4 mg/m² from 6 mg/m² in the EORTC study.

The aim of this interim report was to assess the feasibility and local control probability of this concurrent chemoradiotherapy in a multi-center trial.

PATIENTS AND METHODS

1. Eligibility criteria

Eligibility criteria included the following: histologic or cytologic confirmation of NSCLC, unresectable stage IIIA or stage IIIB, no prior chemotherapy or radiotherapy, age more than 20 years and less than 80 years, performance status less than 3 on the Eastern Cooperative Oncology Group

III 非 小細胞 肺腺癌に対する少量cisplatin同時併用放射線療法--中間報告--

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(ECOG) scale, adequate pretreatment bone marrow (WBC count $\geq 3,000/\mu L$, platelet count $\geq 100,000/\mu L$, hemoglobin $\geq 10$ g/dL), adequate hepatic function (serum GOT/GPT $\leq 100$ IU/L, serum total bilirubin $<2.0$ mg/dL), adequate renal function (serum creatinine $\leq 1.2$ mg/dL, creatinine clearance $\geq 60$ mL/min), adequate pulmonary function (partial pressure of arterial oxygen $\geq 70$ mm Hg), normal cardiac functions, measurable lesions, no concurrent active malignancies, and provision of written informed consent. Patients with malignant pleural effusion were excluded. Institutional review board approval of this protocol was required at all participating institutions before registration onto this study.

2. Treatment

External beam radiotherapy was administered with 6-20 MV linear accelerator photons. Treatment fields encompassed the primary tumor with a 1.0-1.5 cm safety margin. Ipsilateral hilar lymph nodes and mediastinal lymph nodes with more than 1.0 cm short axis diameter were encompassed in the treatment field. Continuous course treatment up to a total dose of 66 Gy in 33 daily fractions of 2.0 Gy was delivered over 6.6 weeks to the primary tumor and the involved lymph nodes. The spinal cord dose was limited to 46 Gy by using a multiple field technique or oblique, parallel opposed fields excluding the cord after a dose of 40 Gy.

Chemotherapy consisted of daily cisplatin 4 mg/m$^2$ i.v. infusion with 0.51 saline, which was given 5 days per week (from Monday to Friday) for the first 5 weeks. The infusion started half an hour before radiation.

If grade 4 radiation-induced esophagitis occurred (according to JCOG criteria), radiotherapy was withheld until esophagitis recovered to grade 3. If partial pressure of arterial oxygen worsened more than 10 mm Hg, and dropped under 70 mm Hg, then radiotherapy was stopped.

3. Outcome and statistical analysis

Treatment toxicity was assessed according to the JCOG (Japan Clinical Oncology Group) criteria, which closely corresponds to the WHO grading system. Patients were followed at 3-monthly intervals for 2 years, then every 6 months until tumor progression.

The primary endpoint of this study was local progression-free survival at 2 years after onset of treatment. It was calculated from the first day of treatment using the Kaplan-Meier method. Secondary endpoints were toxicity, tumor response assessed at 4 weeks after completion of treatment, and overall survival. The tumor response was evaluated according to the WHO criteria.

A sample size of 74 patients was planned to provide 2-year survival rate of more than 26% at a significance level, which was reported by the EORTC study.

RESULTS

1. Patient population

From January 1998 to December 1999, 10 eligible patients were enrolled in the study by seven cooperating centers. Patient characteristics were the following: male; 8, female; 2, median age; 69 years (range 37-76), performance status 0; 5, 1; 5. Pathology included 6 squamous cell carcinomas and 4 adenocarcinomas. Six patients had stage IIIA, and 4 patients had stage IIIB.

2. Concurrent chemoradiotherapy

One patient stopped radiotherapy at 50 Gy because of appearance of bone metastasis. One patient received 60 Gy because of misunderstanding of the protocol. The remainder received 66 Gy. All the patients excluding one whose radiotherapy was stopped at 50 Gy received the planned chemotherapy for 5 weeks. The median dose of cisplatin was 150 mg (range 108-200). Full treatment was delivered to 8 patients with no interruption. Median treatment duration was 46.5 days (range 40 ~ 69 days).

3. Toxicity

Toxicity data are shown in Table 1. Because the toxicity record of one patient was missing, it was analyzed for 9 patients. Hematological dysfunction was the most frequent adverse effect but it was not severe and did not interfere with treatment. Grade 2 esophagitis was noted only in one patient. There was no case of radiation pneumonitis $\geq$ grade 2, nor renal insufficiency. There has been reported no case with $\geq$ grade 3 toxicity, nor severe late toxicity.

4. Tumor response and survival

Tumor response was assessed with chest CT scan 4 weeks after treatment was completed. One patient had complete response, 6 had partial response, 2 had stable disease, and 1 had progressive disease, yielding an overall response rate of 70%.

Median follow up of surviving patients was 26.7 months. Overall survival and local progression-free survival are illustrated in Fig.1 and Fig. 2, respectively. Median overall

| Table 1 Acute toxicity according to the JCOG criteria. |
|-----------------|--------------|-------------|------------|
| Nausea/vomiting | 9            | 1 (11%)     | 0          |
| Esophagitis     | 9            | 2 (22%)     | 1 (11%)    |
| Renal insufficiency | 9        | 0           | 0          |
| White blood cell count | 9 | 3 (33%) | 3 (33%) |
| Platelet count  | 9            | 9 (100%)    | 0          |
| Hemoglobin      | 9            | 5 (56%)     | 1 (11%)    |
Fig. 1 Overall survival in patients with stage III NSCLC treated with concurrent chemoradiotherapy using daily low-dose cisplatin.

survival was 14.6 months with 57% at 1 year and 35% at 2 years, respectively. Median local progression-free survival was 8.4 months with 47% at 1 year and 35% at 2 years, respectively.

5. Patterns of failure
At the time of this report two patients were still alive for 8 months and 2 years 3 months. One patient died of intercurrent disease at 8 months.

Of 7 patients with documented progression or recurrence, 3 had distant failure, and 4 had both local and distant failure.

DISCUSSION
During the past 15 years, there has been a clear demonstration of modest survival improvements for patients with stage III NSCLC when treated with a careful combination of currently available radiotherapy and chemotherapy. Several studies using sequential chemotherapy followed by chest radiation document an improvement in survival, compared with radiation alone5, 3). Some other studies using concurrent chemoradiotherapy also show an improvement in survival3, 6, 7). One recent randomized comparative study showed a small but significant survival benefit of concurrent over sequential chemoradiotherapy5). However, the optimal schedule of combining these two treatment modalities has not been established5).

The EORTC study has demonstrated in a randomized trial that daily cisplatin and radiation significantly improve both survival and control of local disease at the price of substantial side effects5). Our study design was fundamentally derived from the EORTC study, however, the schedule was modified with omitting the rest period and reducing the daily radiation and cisplatin dose. In the EORTC study, the incidence of grade 3+4 nausea, esophagitis, and leucocytopenia was 16%, 7% and 8%, respectively7). In this study, 88% of patients were treated as outpatients. Although the incidence of grade 3 toxicity was nearly equal to the EORTC study, they concluded this protocol to be feasible with acceptable toxicity. In our study, however, there was no case with grade 3 toxicity. Although the number of cases are still limited, our study is considered to be feasible with acceptable toxicity.

The 2-year survival rate in the EORTC study and in the Basel study was 26% and 32%, respectively. In our study, the median survival duration was 14.6 months, and the 2-year survival rate was 35%. The local progression-free survival rate at 2-year was also 35%. Although the patient population is still too small, the survival figures seem to be encouraging.

In the study of Jeremic et al the addition of daily low-dose carboplatin and etoposide was significantly better than radiotherapy alone5). In this trial hyperfractionated radiotherapy was used, therefore it should not be directly compared to studies with conventional fractionation. Nevertheless, there seems to be a trend in favor of daily, i.e. truly radiosensitizing chemotherapy.

CONCLUSION
Our concurrent chemoradiotherapy study using daily low-dose cisplatin (4 mg/m²) and conventional radiotherapy up to 66 Gy was considered to be feasible and to have the possibility to offer better local control than radiation alone in the treatment of patients with stage III non-small cell lung cancer. These results will serve as a basis for further improvement of our treatment scheme.

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REFERENCES


要旨：Ⅲ期非小細胞肺癌に対し、総線量66Gy／33回／6.6週の通常分割照射とcisplatin達日少量（4mg/m²）投与の同時併用療法を、厚生省がん研究助成金による多施設共同研究として企画した。これまでに登録された10例について中間解析を行ったところ、grade III以上の有害事象は1例もなく、中間生存期間14.6ヶ月、2年累積生存率35%という結果が得られた。この化学放射線療法は、Ⅲ期非小細胞肺癌に対する有効な治療法の一つになる可能性が示唆された。