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ORIGINAL ARTICLE

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A phase II study of cisplatin, oral administration of etoposide, OK-432 and radiation therapy for inoperable stage III non-small cell lung cancer

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Abstract

Background. This study was designed to evaluate the feasibility and efficiency of giving cisplatin, etoposide, and OK-432 concurrently with conventional radiotherapy (RTx) for patient's with inoperable stage III, based on the TNM classification according to the International Union against Cancer staging system for lung cancer (1987) non-small cell lung cancer (NSCLC).

Methods. From January 1992 to December 1994, 31 patients with cytologically or histologically confirmed stage III NSCLC were treated with RTx, to a total dose of 56–64 Gy, with concurrent daily oral administration of etoposide (25 mg) and cisplatin (20 mg) for 5 days during the third or fourth week from the start of RTx. The subcutaneous injection of 1 or 2 KE of OK-432, three times a week, for the duration of radiotherapy also started from the beginning of RTx.

Results. The number of eligible patients was 29 (26 men and 3 women). Their mean age was 66 years (range, 55–77 years). Six patients had an Eastern Cooperative Oncology Group performance status (PS) of 0; 15, 1; 8; 2. Three were stage IIIA, and 26, stage IIIB. Histologically, 2 had adenocarcinoma, 23, squamous cell carcinoma, and 4, large cell carcinoma. In 27 of the 29 patients, the RTx schedule was completed. There were no treatment-related deaths. Grade 4 toxicity (according to World Health Organisation criteria) leukopenia (700/μl) was observed in 1 patient. The response rate was 79% and the median survival was 17 months. Survival rates at 1, 2 and 3 years were 62%, 31%, and 21%, respectively. The local failure rate was 51%.

Conclusion. The combination of cisplatin, etoposide, and OK-432, given concurrently with conventional RTx is feasible and effective for inoperable stage III NSCLC.

Key words Stage III non-small cell lung cancer · CDDP · VP-16 · Conventional radiotherapy · Concurrent chemo- and radiotherapy · Accelerated proliferation

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Introduction

Patients with stage III non-small cell lung cancer (NSCLC) should be considered for clinical trials because of their poor long-term outcomes thus for. The median survival after radiotherapy alone, with or without modified fractionation, ranges from 9 to 12 months.[1–4] Since the addition of cisplatin to combined chemotherapy, such combined chemotherapy and radiotherapy has been reported to improve survival in prospective clinical studies.[5–8] This may be the most promising strategy for unresectable stage III NSCLC.

Accelerated proliferation was proposed to be the cause of radioresistance in head and neck cancers when the dose requiring local control of 50% of the tumors was plotted against overall treatment time.[9] To obtain the same tumor control probability with prolongation of overall treatment time, when this is more than 4 weeks, the total dose must be increased. The increased dose is needed because of accelerated proliferation of tumor cells. To overcome this problem,

we have used two types of chemotherapy together with standard fractionation.

Since accelerated proliferation is generally observed 3–4 weeks after the initiation of radiotherapy, we added cisplatin, over a 5-day period, in this phase. Further, since accelerated proliferation was observed immediately after the initiation of radiotherapy in an experimental tumor,[10] we administered oral etoposide on a daily basis from the start of the therapy. As our previous study showed that OK-432, a streptococcal preparation, reduced the incidence and severity of thrombocytopenia when combined with oral etoposide and radiotherapy (unpublished data) we included OK-432 in the present combined therapy approach.

This prospective phase II study was conducted to determine the feasibility, toxicity, response rate, and survival with the cisplatin, etoposide, and OK-432 chemotherapy combined with conventional radiotherapy for unresectable stage III non-small cell lung cancer.

Patients and methods

Eligibility criteria

The main patient eligibility criterion was a histologically or cytologically confirmed, previously untreated, unresectable clinical stage IIIA or IIIB NSCLC based on the TNM classification according to the International Union against Cancer staging system for lung cancer (1987). Patients were also required to have measurable or assessable disease, be aged under 80 years, have an Eastern Cooperative Oncology Group performance status (PS) equal to or less than 2 and no active concomitant malignant disease. Patients with malignant effusions were excluded.

Measurable or assessable diseases were determined on the basis of both chest X-rays and computed tomography (CT). Routine staging evaluation was made using CT or magnetic resonance imaging of the brain, CT or ultrasonic examination of the upper abdomen, and bone scintigraphy. Other criteria were white blood cell (WBC) count, ≥4000/μl, platelet count, ≥100000/μl, hemoglobin, ≥10.0 g/dl, serum bilirubin, ≤1.5 mg/dl, serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT), ≤ twice the normal upper limit (8–40/3–40); 24-h creatinine clearance, ≥70 ml/min; and arterial oxygen pressure, ≥70 mmHg. Those with severe concomitant disease (such as collagen disease) were excluded from this study. Informed consent was obtained from all patients.

Therapy

The protocol for the therapy is shown in Fig. 1. Eligible patients were referred to hospitals with a telecobalt unit for the radiotherapy. They were then followed as outpatients or in patients at their original hospitals. Additional treatment was optional and most patients received only palliative therapy (such as; hyperalimentation, pain management etc. 8–40/3–40).

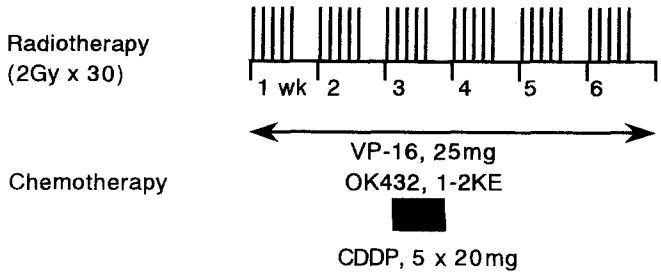

Fig. 1. Treatment schedule of concurrent chemotherapy and radiotherapy for patients with stage III non-small cell lung cancer (NSCLC). *VP-16*, Etoposide; *CDDP*, cisplatin

Conventional radiotherapy was delivered by telecobalt units with a fraction size of 2 Gy, 5 days a week, for a total dose of 60–64 Gy. There were no corrections for lung inhomogeneity. Initial fields covered the primary lesions and the mediastinum where lymph nodes were enlarged. Radiation fields were outlined 1–2 cm outside the tumor margin. The supraclavicular and contralateral hilar nodes were included only when enlarged tumor was observed in these regions. At 40–44 Gy, the initial field was changed to a small field with oblique, parallel opposite beams to spare the spinal cord.

Cisplatin was given, at 20 mg daily, intravenously for 5 days during the third or fourth week after the start of radiotherapy. The patients were moved to the radiation room for radiotherapy within less than 1 h after the completion of each cisplatin administration. Adequate hydration was provided throughout the treatment period. Anti-emetics such as metoclopramide, steroids, and ondansetron were administered when the patients suffered from nausea, vomiting, and anorexia during the cisplatin administration. Twenty-five mg of etoposide was given orally every morning from the start of therapy to the end. In addition, one or two KE of OK-432 was injected subcutaneously three times a week until the end of the therapy.

Toxicity

Toxicity grading, with leukocyte and platelet counts, was done according to World Health Organisation (WHO) criteria. When marrow suppression was observed (e.g., grades 2–3 leukopenia or grade 1–2 thrombocytopenia) etoposide was withdrawn. When grade 4 leukopenia or grade 3 thrombocytopenia was observed, both the chemo- and radiotherapy were withdrawn. When grade 2–4 leukopenia was observed, granulocyte colony stimulating factor (G-CSF) was administered for 7–10 days in place of OK-432.

Toxicity grading of esophagitis was done according to our criteria: grade 0, no symptoms; grade 1; pain on swallowing, with no need for medication; grade 2, necessity for medication to ease pain on swallowing or difficulty in swallowing; grade 3, no solid food intake – liquid alimentation; grade 4, as no water intake – intravenous hyperalimentation or liquid alimentation via a naso-gastric tube. If grade 3–4

toxicity was observed, chemo- and radiotherapies were withheld until esophagitis recovered to grade 2 or less.

When clinical symptoms and signs from chest X-rays, CT scans, and laboratory data revealed radiation pneumonitis, chemo- and radiotherapies were discontinued. Treatment of radiation pneumonitis took priority over cancer treatment.

Late lung toxicity was evaluated by internal reviews on a case-by-case basis. However, we could not confirm lung damage for three patients, as they were referred to other hospitals distant from our district and sufficient radiological examinations could not be performed. Pneumonitis and fibrosis were differentiated by chest X-rays and/or chest CT films, with consideration of symptoms. Because of the difficulties in scoring of lung toxicities because of the multicentric patient care, we considered only the incidence of radiation pneumonitis and fibrosis in this study.

Response

Responses, evaluated according to WHO criteria, compared findings immediately before therapy and 4 weeks after end of the therapy. A complete response (CR) was the disappearance of tumor for at least 4 weeks. A partial response (PR) was a decrease of 50% or more in the size of the tumor. Progressive disease (PD) was defined as ≥25% increase in tumor size or the appearance of new lesions.

Statistical analysis

Survival was calculated based on the period from the start of treatment to death or the last follow-up evaluation. Survival curves were plotted by the method of Kaplan and Meier.[11] The last follow-up was July 16, 1997 and the last review was July 26, 1997.

Results

Patient characteristics

The patient profile is given in Table 1. From January 1992 to December 1994, 31 patients entered the study. Of these, 2 were excluded after review because of a stage IV diagnosis, i.e., metastases demonstrated retrospectively. Ninety percent of the eligible patients were men. Squamous cell carcinomas were more frequent (79%) than adenocarcinomas (7%) and large cell carcinomas (14%). Ten percent of the patients had stage IIIA and 90% of patients had stage IIIB disease. T4N2 disease was the most frequent (59%). Most of the patients (72 %) had a PS equal to or less than 1.

Table 1. Patient characteristics

No. of patients entered	31
No. of eligible patients	29
Average age of eligible patients (years)	66
Range (years)	55–77
Gender	
Male	26
Female	3
Histology	
Adenocarcinoma	2
Squamous cell carcinoma	23
Large cell carcinoma	4
Clinical stage[a]	
IIIA	3
IIIB	26
TNM classification[b]	
T2N2	1
T2N3	1
T3N2	1
T3N3	1
T4N1	4
T4N2	17
T4N3	4
Performance status[c]	
0	6
1	15
2	8

[a,b] Based on TNM classificational of International Union against Cancer (1987).
[c] According to Eastern Cooperative Oncology Group classification.

Compliance and toxicity

All but two of the eligible patients received 56–64 Gy (median total dose, 60 Gy). Of the two other patients, one received only 40 Gy, with radiotherapy then being stopped because of severe preexisting pulmonary fibrosis, and the other refused further treatment. However, these two patients received the full intended dose of cisplatin and two-thirds of the intended dose of etoposide. They died after 6 and 41 months, respectively.

All patients received the full intended dose of cisplatin. Not all patients received the full dose of the etoposide protocol, because of marrow toxicity and renal dysfunction. The administration period ranged from 15 to 49 days (median, 39 days).

There was no interruption of the treatment protocol because of acute toxicities.

Toxicity findings are summarized in Table 2. One patient had grade 4 leukopenia but none demonstrated grade 4 for thrombocytopenia or esophagitis. One patient had grade 2 and one had grade 3 thrombocytopenia and 25 complained of esophagitis-related symptoms. There were no treatment-related deaths. One patient, with a history of apoplexy, developed intractable peripheral neuropathy and one patient had mild renal dysfunction. No severe lung toxicity (i.e., that requiring continuous oxygen therapy) was observed. All patients who developed pneumonitis subsequently demonstrated radiation fibrosis. Even at this stage, however, no severe lung toxicity was observed. No chronic esophagitis was encountered.

Response and survival

Tumor response was assessed based on radiography, with chest X-rays and CT scans available for comparison. Two patients were evaluated as achieving CR and 21 as achiev-

Table 2. Toxicity findings

WBC[a]	
Leukopenia, grade 2	11 (38%)
Leukopenia, grade 3	8 (28%)
Leukopenia, grade 4	1 (3%)
Platelets[b]	
Thrombocytopenia, grade 2	1 (3%)
Thrombocytopenia, grade 3	1 (3%)
Thrombocytopenia, grade 4	0 (0%)
Esophagitis[c]	
Grade 2	11 (38%)
Grade 3	2 (7%)
Grade 4	0 (0%)
Incidence of radiation pneumonitis[d]	8 (32%)
Incidence of radiation fibrosis[d]	14 (56%)
Intractable peripheral neuropathy	1 (3%)
Renal dysfunction (Cr < 2 mg/dl)	1 (3%)

[a,b] According to World Health Organisation criteria.
[c] See details in text.
[d] Determined in 25 patients due to insufficient data.

Table 3. First sites of failure

Local recurrence	14 (48%)
Regional recurrence	2 (7%)
Distant metastasis	4 (14%)
Local recurrence + distant metastasis	1 (3%)
Regional recurrence + distant metastasis	2 (7%)
Dead, other disease	2 (7%)
Alive	4 (14%)

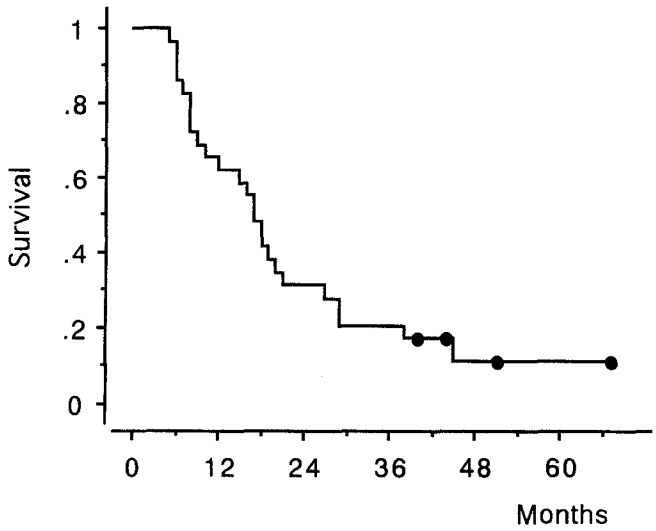

Fig. 2. Survival of 29 patients with stage III NSCLC treated by regimen shown in *Fig. 1.* ●, censored data

ing PR. The response rate was thus 79% (23/29). The six remaining patients were evaluated as showing NC; there was no PD. The survival curve for the eligible patients is shown in Fig. 2. The probability of survival was calculated and the overall median survival was 17 months. Survival rates after 1, 2 and 3 years were 62%, 31%, and 21%, respectively. Of the five patients who lived more than 3 years, four were still alive with no evidence of local recurrence nor distant metastasis. The average age of these four patients was 62 years (range 58–68 years; and three were PS 2 while one was PS 1. All four were stage IIIB; three had squamous cell carcinoma 3, and one had large cell carcinoma. Of the eight eligible PS 2 patients, two had long survival more than 4 years (i.e., 67 and 51 months).

Patterns of failure

The first sites of failure are listed in Table 3. Fifteen patients (51%) had local recurrence with or without metastasis and 7 patients (24%) had distant metastasis with or without local or regional recurrence. Of those with distant metastases, 4 had brain lesions. One patient died because of progression of preexisting pulmonary fibrosis and one patient died because of tumor-unrelated cachexia associated with progressive dementia occurring after cerebral infarction.

Discussion

Recent results of phase I/II studies with combined chemotherapy and radiotherapy for stage III NSCLC have been promising.[12–15] Median survival times were 14–19 months, with a 2-year survival rate of 30%–40% for eligible patients, similar to results in our study. The 21% survival rate after 3 years in the present study was particularly encouraging.

The level of toxicity in our study was tolerable and all but two patients completed the protocol. There were no treatment-related deaths and only one patient with leukopenia demonstrating grade 4 toxicity. In another study using oral etoposide, cisplatin, and hyperfractionated radiotherapy, greater toxicity was encountered; 57% of the patients developed grade 4 hematologic disease and 53% had grade 3 or 4 esophagitis.[16] In contrast to our study, that study employed two cycles of oral etoposide (50 mg b.i.d. for 14 days) and cisplatin (50 mg/m^2 days 1 and 8) during 6 weeks of conventional radiotherapy (69.6 Gy; 1.2 Gy b.i.d.). Thus there were differences in both the intensity of chemotherapy and in the fractionation. In terms of acute toxicity, a total dose of 69.6 Gy with 1.2 Gy twice daily is equivalent to a total dose of 64–65 Gy with 2 Gy once daily when an α/β ratio of 10 Gy is used for correction of fraction size.[17]

Accelerated repopulation is considered to be the main reason for radioresistance. To overcome this, two approaches are employed. One is to shorten overall treatment time as much as possible[18–20] using accelerated fractionation, such as continuous hyperfractionated accelerated fractionation (CHART). A randomized phase III study comparing CHART with conventional radiotherapy for NSCLC also showed significantly better results with the CHART.[20] The other is to overlap concomitant boost radiotherapy during the course of conventional radiotherapy.[21,22] In this case, with better treatment results obtained when the boost is given during the last 2–21/2 weeks, rather than during the first 2–21/2 weeks.[22] This result indicates the importance of

timing to give accelerated fractionation. Thus, the therapy aimed at eliminating proliferating cells at the phase of repopulation is an important strategy for treatment of resistant tumors.

Our present study featured two-way intervention in the accelerated repopulation phase; weighted chemotherapy at the time of initiation of repopulation and another continuous low-dose chemotherapy throughout the radiation period. This distinguishes our protocol from those employed in previous studies in which only one cycle of chemotherapy was used, although some phase I/II studies of combined chemo- and radiotherapy have consisted of at least two cycles of chemotherapy.[12–16,23] The incidence of local failure (51%) in our present study was relatively high compared with the range of 4%–40% reported earlier,[12–16,23] but this may be, in part, a reflection of the high incidence of squamous cell carcinomas in our cohort (79%). However, the combination was very effective in some patients, and further improvement to the treatment protocol is clearly possible.

OK-432, an extract of streptococcal pyrogens, was hoped to have major anti-cancer effects, but clinical studies in cancer patients have been disappointing. However, the action of OK-432 in controlling bone marrow toxicity was recently noted.[24,25] After introduction of G-CSF, leukopenia could be easily handled in many cases but thrombocytopenia is still a problem. Our earlier unpublished data indicated that OK-432 decreased the incidence of thrombocytopenia induced by radiation therapy when given concomitantly with etoposide.

In conclusion, we report promising results with a combination of cisplatin, etoposide, and OK-432 given concurrently with conventional radiotherapy for inoperable stage III NSCLC. The results point to an effective new strategy to overcome the accelerated repopulation that is one cause of radioresistance. Phase I/II studies aimed at improvement of local control are clearly warranted.

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