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# CISPLATIN, ETOPOSIDE, AND VINCRISTINE COMBINATION CHEMOTHERAPY IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER

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## ABSTRACT

Thirty patients with previously untreated, inoperable non-small cell lung cancer (NSCLC) were treated with cisplatin, etoposide and vincristine. Among twenty-nine evaluable patients, eight patients achieved partial response and the overall response rate was 28%. No patient achieved a complete response. The median survival time was 51 weeks. Myelosuppression was the dose-limiting toxicity. Four patients had a leukocyte nadir of less than 1000/mm$^3$, and one died from severe myelosuppression and sepsis. The other toxicities were nausea/vomiting, peripheral neuropathy, and alopecia. We conclude that cisplatin, etoposide, and vincristine combination chemotherapy offers moderate activity for inoperable non-small cell lung cancer.

Key Words: Chemotherapy, Non-Small Cell Lung Cancer, Cisplatin, Etoposide, Vincristine

## INTRODUCTION

Treatment of advanced non-small cell lung cancer (NSCLC) is a great challenge to clinicians caring for patients with this malignancy. Surgical treatment yields favorable results only in stage I or II disease.[1)] Systemic chemotherapy, therefore, should play an important role in the management of advanced NSCLC. Cisplatin combined with vinca alkaloid has been reported to have a good response rate.[2)] However, this improved response rate has not been translated into a beneficial effect on survival.[3)] Hence, the development of a more active combination chemotherapy for NSCLC continues to be necessary. Etoposide is also one of the active agents against NSCLC. Phase II studies of etoposide in NSCLC have shown tumor regression rates of nearly 20%. Etoposide combined with cisplatin has demonstrated synergistic therapeutic activity in both animal studies and clinical trials.[4–6)] Longeval et al.[5)] reported an objective response rate of 38% against NSCLC using the combination of etoposide and cisplatin. Vincristine, as a single agent, has been used with a response rate of approximately 12% in non-small cell lung cancer.[7,8)] In spite of a lower response rate compared with other vinca alkaloids, vincristine has relatively less myelosuppressive effect, therefore can be combined with other myelosuppressive drugs more easily. In light of these results, we undertook combination chemotherapy consisting of cisplatin, etoposide, and vincristine for untreated, inoperable non-small cell lung cancer.

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## PATIENTS AND METHODS

From February 1984 to March 1985, thirty patients with non-small cell lung cancer were entered on this multiinstitutional clinical study. Participating institutions are listed in Table 1. All patients had histologically confirmed inoperable non-small cell carcinoma of the lung. Six had stage II disease, 7 had IIIA, 2 had IIIB, and 14 had stage IV disease. All six patients with stage II disease were technically inoperable because of their poor pulmonary functions. The following criteria were used for entry in this study: 1) age less than 80 years; 2) Eastern Cooperative Oncology Group (ECOG) performance status of less than 3; 3) no prior chemotherapy, radiotherapy, or surgery; 4) measurable or evaluable lesions on chest X-ray; 5) WBC$>4000/mm^3$, RBC$>350\times10^4/mm^3$, platelet count$>10\times10^4/mm^3$; 6) creatinine clearance$>60$ ml/min, serum creatinine$<1.5$ mg/dl; 7) total serum bilirubin$<2$ mg/dl, SGOT and SGPT less than four times the normal range; and 8) no active disease in other organs. Pretreatment evaluation consisted of history, physical examination, chest X-ray in posteroanterior and lateral view, lung tomogram, chest CT scan, upper abdominal ultrasonography or CT scan, complete blood cell count, blood chemistry profile, ECG, 24-hour urine collection for creatinine clearance and urinalysis. Cranial CT scan was performed if a patient was clinically suspected for metastatic brain lesion. Physical examination, chest X-ray, complete blood cell count, blood chemistry, serum electrolytes, and urinalysis were obtained every week. Twenty-four hour urine collection for creatinine clearance was repeated before every infusion of cisplatin. The treatment schedule was cisplatin (60 mg/$m^2$, day 1), etoposide (60 mg/$m^2$, days 1–4), and vincristine (1 mg/$m^2$, days 1 and 8). This regimen was repeated every 4 weeks and was continued until there was evidence of progressive disease or unacceptable toxicity. Cisplatin, at a dose of 60 mg/$m^2$, was given over 60 minutes on day 1. Patients received 1000 ml of Ringer's solution for pre- and post-hydration with furosemide and mannitol. Therapeutic responses were defined as follows: complete response (CR) — disappearance of all known disease for at least 4 weeks; partial response (PR) — more than 50% reduction in the product of perpendicular diameters in measurable disease for at least 4 weeks, or an estimated decrease of more than 50% for evaluable lesions; no change (NC) — less than 50% reduction or less than 25% progression without appearance of new lesions for at least 4 weeks; and progressive disease (PD) — more than 25% increase or appearance of new lesions. The analysis of patient survival time was done by the method of Kaplan and Meier, and the generalized Wilcoxon test.

Table 1. Participating Institutions

| |
|---|
| Aichi Prefectural Hospital |
| Japanese Red Cross Nagoya First Hospital |
| Meitetsu Hospital |
| Nagoya Ekisaikai Hospital |
| Nagoya University Hospital |
| National Chubu Hospital |
| Tokai Central Hospital |

## RESULTS

Among the 30 patients entered on this study, 29 were considered evaluable for therapeutic response. One patient died early in the treatment course because of severe neutropenia but was

Table 2. Patient Characteristics

| | No. of patients |
|---|---|
| Entered/Evaluable | 30/29 |
| Median age in yrs (range) | 68 (42–79) |
| Sex | |
| Male | 22 |
| Female | 7 |
| Performance status (ECOG) | |
| 0–1 | 25 |
| 2–3 | 4 |
| Histologic cell type | |
| Squamous cell carcinoma | 14 |
| Adenocarcinoma | 14 |
| Large cell carcinoma | 1 |
| Stage | |
| II | 6 |
| IIIA | 7 |
| IIIB | 2 |
| IV | 14 |

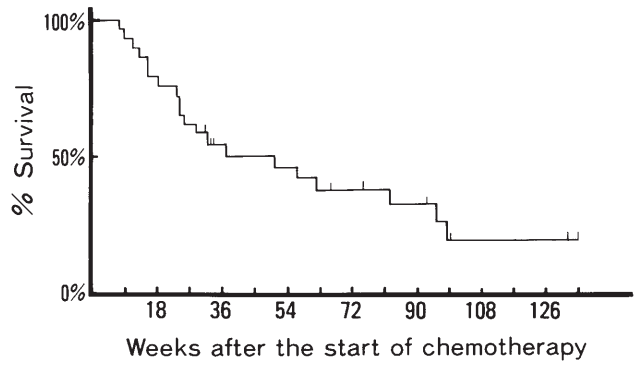


Fig. 1. Survial curve from the initiation of chemotherapy for all patients
Tick mark indicates last follow up.

included in the analysis of toxicities. Patient characteristics are shown in Table 2. Among the 29 evaluable patients, eight achieved partial responses (five adenocarcinoma, two squamous cell carcinoma, and one large cell carcinoma), and the response rate was 28%. No patient achieved complete response. The most of tumor regression of more than 50% was observed within 3 weeks after the initiation of chemotherapy. The median duration of response was 12 weeks (range 5 to 94+ weeks). The median survival time was 51 weeks (Fig. 1). After exclusion of stage II patients, the median survival time was 50 weeks.

Toxicities were summarized in Table 3. Among the 30 patients evaluable for toxicities, four (13.3%) had a leukocyte count nadir of less than 1000/mm$^3$. There was one early death (17 days after the initiation of chemotherapy) from severe myelosuppression and sepsis. Five (17%) patients had a platelet count nadir of less than 50000/mm$^3$. Twenty-seven (90%) patients had a fall in hemoglobin of more than 2 g/dl. One patient who presented with moderate anemia (RBC nadir = $250\times10^4$/mm$^3$) received a blood transfusion. Other major toxicities were nausea and/or vomiting, azotemia, peripheral neuropathy, and alopecia. Azotemia, defined as an increase of serum creatinine level$>$1.5 mg/dl, occurred in 10% of patients. Azotemia was transient and subsided before the next treatment. Twenty patients who experienced nausea and/or vomiting were treated with concomitant administration of antiemetics and/or glucocorticoids. Peripheral neuropathy occurred in seven cases but did not require a dose reduction of vincristine.

Table 3. Toxicities in 30 Patients

| | No. of patients |
|---|---|
| Leukocyte count naidr (/mm$^3$) | |
| 2,000–3,900 | 11 (36.7%) |
| 1,000–1,900 | 12 (40.0%) |
| $<$1,000 | 4 (13.3%) |
| Platelet count nadir (/mm$^3$) | |
| 50,000–99,000 | 2 ( 6.7%) |
| $<$50,000 | 5 (16.7%) |
| Fall in hemoglobin (g/dl) | |
| $>$2.0 | 27 (90.0%) |
| Nausea and/or vomiting | 20 (66.7%) |
| Maximum serum creatinine (mg/dl) | |
| 1.5–2.0 | 2 ( 6.7%) |
| $>$2.0 | 1 ( 3.3%) |
| Peripheral neuropathy | 7 (23.3%) |
| Alopecia | 20 (66.7%) |

## DISCUSSION

Prognosis of advanced non-small cell lung cancer is still poor. Various combination chemotherapies including cisplatin have been introduced and obtained modest activity.[9] But survival itself has not been prolonged as much as we expected. The present study revealed that the response rate of 28% for the cisplatin, etoposide, and vincristine combination regimen was comparable with those of reported studies.[10,11] Bertrand et al.[10] reported a response rate of 27% to the combination of etoposide, vincristine, and cisplatin. Kaplon et al.[11] also reported a response rate of 24% to the combination of these three agents. Furthermore, the combination of etoposide and cisplatin without vincristine also showed a similar response rate. The European Organization for the Research and Treatment of Cancer (EORTC) has found a response rate of 38% for the combination of etoposide and cisplatin.[5] Dhingra et al.[12] showed a response rate of

30% for the combination of etoposide and cisplatin. Vincristine combined with 5-flurouracil and mitomycin C was reported to have a response rate of 41% in advanced NSCLC.[13] The activities of combination chemotherapy regimens including vincristine were reviewed by Sorensen et al.[14] In a recent paper, Murray et al.[15] reported a weekly CODE (Cisplatin, Vincristine, Doxorubicin, and Etoposide) regimen for non-small cell lung cancer that included vincristine. They referred to Sorensen's paper[14], and commented that substitutions of a more established vinca alkaloid, such as vinblastine and vindesine, at full doses may not be feasible. We used vincristine in this study because it had relatively less myelosuppressive effect compared with other vinca alkaloids. Our results suggest that the administration of vincristine in combination with cisplatin did not improve the response rate in patients with NSCLC.

The median survival time of 51 weeks for the present regimen seems to be better than that for the combination of etoposide and cisplatin.[5,12] This difference might be due to the fact that most of the patients treated with the present combination regimen had good prognostic factors such as performance status and disease extent.

The dose-limiting toxicity of this regimen is myelosuppression. Four of the 30 patients had a leukocyte count nadir of less than $1000/mm^3$, and five patients experienced thrombocytopenia of less than $50000/mm^3$. One patient died of sepsis. Other toxicities were mild and well tolerated.

In conclusion, cisplatin, etoposide, and vincristine combination chemotherapy provide moderate acitivity in the treatment of non-small cell lung cancer. The addition of vincristine seems to provide no advantage.

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