Response to Combined Modality Treatment in a Five-year Survivor of Extensive Small Cell Lung Cancer with Severe Complications

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Abstract

We present a rare case of a five-year survivor of small cell lung cancer with severe complications who responded to combined modality treatment. Prior to initial chemotherapy, he experienced severe complications including sepsis, pneumonia, ileus, and a performance status of 4. He was treated with an ileus tube and IVH, and was managed by mechanical ventilation for four days. After his general condition improved, he received combination chemotherapy of carboplatin, with the target area under the plasma concentration versus the time curve (AUC) of 5 mg · min/ml day 1, and etoposide (80 mg/m²) on days 1, 2, 3 for four courses, and complete remission (CR) was obtained. Six months later, systemic relapse occurred, but he achieved complete remission again with nine courses of CODE (cisplatin, vincristine, adriamycin, and etoposide) chemotherapy and sequential chest radiotherapy. Five years after the initial chemotherapy, the patient is alive and disease free.

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Key words: small cell lung cancer, poor risk, chemotherapy, radiation therapy, long-term survivor

Introduction

Lung cancer is the leading cause of cancer mortality for males in Japan, and it is expected to become so for females. Approximately 20% of cases of lung cancer are small cell lung cancer (SCLC). SCLC is highly sensitive to chemotherapy, and combination chemotherapy is the base of treatment. Despite marked responses to initial treatment, almost all patients with extensive disease (ED)-SCLC, and more than 80% of those with limited disease (LD) die of recurrent disease within 3 years

(1). We describe here a male who has survived for five years after diagnosis of ED-SCLC.

Case Report

A 64-year-old man visited a doctor's office complaining of a dry cough and hoarseness from August 1993. Bilateral hilar lymphadenopathy was detected on chest X-ray, and he was admitted to our hospital on August 31 1993. He had smoked 40 cigarettes a day for 40 years. His mother died from lung cancer, and his younger brother had myocardial infarction. On admission, the patient was afebrile and he had no rale in his lungs. Laboratory studies showed elevations of white blood cells (WBC) and lactate dehydrogenase (LDH), and other data reflected normal values. In tumor marker analysis, the levels of neuron specific enolase (NSE) and carcinoembryonic antigen (CEA) were elevated (Table 1). On chest radiography in 1992, no abnormal shadows were evident. Chest radiography on admission showed bilateral hilar and mediastinal lymphadenopathy (Fig. 1). In addition, chest computed tomography (CT) scan revealed invasion of the left atrium by the primary mass of the right lower lobe (Fig. 2). As no endobronchial invasion by the tumor was observed in the bronchofiberscopic examination, transbronchial aspiration cytology (TBAC) of subcarinal lymph node (#7) was performed. The cytology indicated class V of typical SCLC (Fig. 3). Bone scan was positive in the lumbar spine (L5), and lumbar radiography was characteristic of bone metastasis with osteolytic change. Therefore, we made a diagnosis of ED-SCLC with a TNM classification of T4N3M1, and we considered the primary tumor to be the mass with the mediastinal lymph node in the right lower lobe. The clinical course after admission is shown in Fig. 4. After admission, he complained of a full feeling in the abdominal region, which rapidly worsened. One week after admission, he developed ileus, and an ileus tube was inserted for 11 days. Furthermore, he went into critical condition with a performance status (PS) of 4. At the same time, he had pneumonia in the left lobe with septic

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shock, and was managed by mechanical respiration for 4 days. Although blood culture was negative, sputum culture was positive for *Xanthomonas maltophilia* and *Enterobacter aerogenes*. After receiving full supportive care such as continuous catecholamine infusion, intravenous hyperalimentation (IVH), and antibiotic therapy, the severe complications of ileus, pneumonia, and sepsis were all ameliorated, and PS was 3. Therefore, the combination chemotherapy of carboplatin with the target area under the plasma concentration versus the time curve (AUC) of 5 mg · min/ml i.v. day 1 and etoposide (80 mg/m²) i.v. days 1, 2, 3 was started on October 14. Because of grade 4 hematological toxicity during the first course, carboplatin and etoposide were reduced by 25% for subsequent courses. The same toxicities were not observed in up to four courses. After

Table 1. Laboratory Findings on Admission

Peripheral blood	
WBC	8,200/mm ³
RBC	431×10 ⁴ /mm ³
Hb	14.7 g/dl
Ht.	42.2%
Plt	27.7×10 ⁴ /mm ³
Blood chemistry	
Glucose	107 mg/dl
total bilirubin (T. Bil.)	0.5 mg/dl
aspartate aminotransferase (AST)	15 IU/l
alanine aminotransferase (ALT)	13 IU/l
γ-glutamyl transpeptidase (γ-GTP)	55 IU/l
lactic acid dehydrogenase (LDH)	526 IU/l
creatinine kinase (CK)	161 IU/l
total cholesterol (T. Chol.)	206 mg/dl
triglyceride (TG)	180 mg/dl
alkaline phosphatase (ALP)	106 IU/l
total protein (TP)	6.9 g/dl
Albumin	4.3 g/dl
blood urea nitrogen (BUN)	12.4 mg/dl
Creatinin	0.80 mg/dl
Na	143 mEq/l
K	4.0 mEq/l
Cl	104 mEq/l
Ca	8.8 mg/dl
IP	3.5 mg/dl
Amylase	40 IU/l
C-reactive protein (CRP)	0.6 mg/dl
Tumor marker	
squamous cell carcinoma antigen (SCC)	1.5 ng/ml
carcinoembryonic antigen (CEA)	5.3 ng/ml
neuron specific enolase (NSE)	21 ng/ml
α-fetoprotein (AFP)	2.4 ng/ml

Figure 1. Chest radiography on admission showed bilateral hilar and mediastinal lymphadenopathy.

Figure 2. Chest CT on admission revealed bilateral hilar and mediastinal lymphadenopathy and invasion of the left atrium by a primary mass of the right lower lobe.

four courses of chemotherapy, re-staging examinations revealed complete remission (CR), and the PS score was zero, so he was discharged from the hospital on January 31, 1994.

After that, he was seen on an outpatient basis for course observation. On July 27, 1994, his right supraclavicular lymph node was swollen, and a bone scan again revealed uptake in L5. Chest CT revealed swelling of pretracheal lymph node (#3) and primary enlargement. NSE and CEA were not elevated and bronchofiberscopy was not performed, but based on his clinical course, we suspected a relapse. On August 8, 1994, he was admitted to our hospital. He received a total of 9 courses

of CODE regimen therapy consisting of cisplatin, vincristine, adriamycin, and etoposide. After chemotherapy, although uptake in the bone scan, primary lesion, and pretracheal lymph node (#3) swelling in chest CT had disappeared, subaortic lymph node (#5) swelling was thought to be indicative of a new lesion. We made a diagnosis of progressive disease (PD). However, because his general condition was good and only one active lesion was observed, a total of 56 Gy of radiotherapy was irradiated to lymph node #5. After radiotherapy, the focus lesion disappeared from chest CT, and complete remission was obtained again. After that, he was seen on an outpatient basis for course observation again. Five years after the initial chemotherapy, the patient is alive and disease free.

Figure 3. Transbronchial aspiration cytology (TBAC) from subcarinal lymph node (#7) (Papanicolaou stain, ×100).

Discussion

In general, SCLC progresses rapidly. Because metastasis to the whole body from an early stage is common, if chemotherapy is not performed, the prognosis of SCLC patients is extremely poor. ED-SCLC cases with remote metastases have no indications of operation or radiation therapy. Therefore, systemic chemotherapy and radiation therapy are currently the main therapeutic choice for most patients with LD and some with ED (1–4). Of all types of lung cancer, SCLC is the one most effectively treated by chemotherapy. In the literature, the 5-year survival rate of patients with performance status 0 or 1 and localized small cell lung cancer who underwent chemotherapy was 5.3% (5). The five-year survival rate of patients with ED-SCLC is only 1%, and most patients die within two years due to relapse (6).

Poor prognostic factors in SCLC, based upon the Cox pro-

Figure 4. Clinical course after admission.

portional hazard model, are PS (2–4), clinical stage (ED), LDH (≥ 400 IU/l), NSE (≥ 10.0 ng/ml) and WBC ($\geq 8,000/\mu\text{l}$) (3, 5–7). Among these poor prognostic factors, PS is the most important factor (8–10). On the first admission, the present patient had several poor prognostic factors in SCLC such as poor PS, elevation of LDH, extensive disease, and elevation of NSE. Therefore, this patient was considered to have a poor prognosis. Treatment reports of patients with performance status 3 or 4 and extensive small cell lung cancer are extremely rare. Kudo et al treated 16 previously untreated ED-SCLC patients with PS of ≥ 3 with combination chemotherapy of cisplatin (CDDP) (30 mg/m²), cyclophosphamide (CPA) (200 mg/m²), vincristine (VCR) (1 mg/body), adriamycin (ADM) (20 mg/m²), nimustin (ACNU) (30 mg/m²), mitomycin C (MMC) (3 mg/m²). For an average of 2.5 courses of chemotherapy, the response rate was 75%. However, a poor median survival (3.7 months) was reported in that study (11).

In the present case, after admission to our hospital, the patient's performance status went down to 4 because of ileus. Although no radiographic evidence was observed, he had possible mesenteric lymph node metastasis, which developed into ileus. Therefore, the patient could not receive chemotherapy and could receive only supportive care. However, he recovered from pneumonia, sepsis, and ileus, and his performance status increased to 3 by intensive supportive care, so he was able to start the first course of chemotherapy. Because he was considered to be a poor risk, four courses of AUC-based carboplatin and etoposide, in place of CDDP and etoposide with strong toxicity, were performed. The combination of AUC-based carboplatin and a standard dose of intravenous etoposide is an active and relatively non-toxic regimen. In a study using this regimen, the response rate was 75%, the median survival time was 10.8 months, and the 1- and 2-year survival rates were 47.2% and 15.4% (3). As a result of carboplatin and etoposide therapy, the present patient achieved complete remission and a PS score of 0. Considering the clinical course, we think that this was a very rare case.

CODE is a well-designed weekly chemotherapy regimen. The four drugs have different mechanisms of action, and their toxicities do not overlap. It has been reported that the overall response rate was 94%, the CR rate 40%, the 2-year survival rate 30%, and the 5-year survival rate 9% for previously untreated patients with ED-SCLC (12, 13). The overall response rate of 88% and CR rate of 29% have been reported for relapsed SCLC patients. Therefore, the CODE regimen is efficacious for treatment of relapsed SCLC (2).

Although the present patient experienced systemic relapse

three months after the first course of chemotherapy, nine courses of CODE chemotherapy were performed, and sequential radiation therapy for a residual lesion was performed. He had ED-SCLC, but his residual tumor was limited to radiation therapy field. Therefore, he maintained complete remission for a long time. In ED-SCLC, as in this case, previously untreated patients with a PS of 4 are not rare. It is very important to improve a PS of 4 to 3, and to treat severe complications so that the patient can receive chemotherapy with curative intention. We reported here an extremely rare case in which a patient overcame ED-SCLC with severe complications and then survived for more than 5 years.

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