Double-Cycle, High-Dose Ifosfamide, Carboplatin, and Etoposide Followed by Peripheral Blood Stem-Cell Transplantation for Small Cell Lung Cancer*

Yoshinobu Iwasaki, MD, PhD; Kazuhiro Nagata, MD; Masaki Nakanishi, MD; Atsushi Natuhara, MD; Yutaka Kubota, MD; Mikio Ueda, MD; Taichiro Arimoto, MD, PhD; and Hiroshi Hara, MD, PhD

Purpose: **To determine the tolerability and feasibility of double-cycle, high-dose chemotherapy followed by peripheral blood stem-cell transplantation (PBSCT) after conventional chemotherapy or chemoradiotherapy for small cell lung cancer (SCLC).**

Patients and methods: **Patients with previously untreated SCLC received two cycles of cisplatin, 80 mg/m^2, and etoposide, 300 mg/m^2 (cisplatin-etoposide [PE]). Later, they were administered high-dose etoposide, 1,500 mg/m^2, followed by granulocyte colony-stimulating factor for collection of peripheral blood stem cells. After two additional cycles of PE, the patients received high-dose ifosfamide, 10 g/m^2, carboplatin, 1,200 mg/m^2, and etoposide, 1,000 mg/m^2 (ifosfamide-carboplatin-etoposide [ICE]) followed by PBSCT twice at 3-month to 4-month intervals. Patients with limited disease (LD) concurrently received 50 Gy of irradiation with the last two cycles of PE.**

Results: **Eighteen patients, including 11 patients with LD, were enrolled. Fifteen patients could receive high-dose ICE followed by PBSCT twice, and 3 patients could receive it once. The median number of CD34+ cells collected was 13.11 × 10^6/kg. The median numbers of days to neutrophil counts ≥ 500/μL and platelet counts ≥ 50,000/μL were 10 days and 14.5 days after the first PBSCT, and 10 days and 15 days after the second PBSCT, respectively. Grade 3 diarrhea occurred in one cycle, and grade 3 renal toxicity occurred in two cycles. The overall response rate was 100%, with an 83.3% rate of complete or near-complete response. The 2-year and 5-year survival rates were 72% and 55% in patients with LD and 43% and 0% in patients with extensive disease, respectively.**

Conclusion: **Double-cycle, high-dose ICE therapy followed by PBSCT is tolerable and feasible even after conventional chemotherapy or chemoradiotherapy in patients with SCLC.**

(CHEST 2005; 128:2268–2273)

Key words: high-dose chemotherapy; peripheral blood stem-cell transplantation; small cell lung cancer

Abbreviations: ABMT = autologous bone marrow transplantation; CR = complete response; ED = extensive disease; G-CSF = granulocyte colony-stimulating factor; ICE = ifosfamide-carboplatin-etoposide; LD = limited disease; nCR = near complete response; PBSC = peripheral blood stem cell; PBSCT = peripheral blood stem-cell transplantation; PE = cisplatin-etoposide; PR = partial response; SCLC = small cell lung cancer

Combination chemotherapy with cisplatin and etoposide (cisplatin-etoposide [PE]) has long been the mainstay of treatment for small cell lung cancer (SCLC). Response rates in extensive disease (ED) range from 51 to 78%, including a 7 to 13% rate of complete response (CR) and a median survival of 8 to 9 months. In patients with limited disease (LD), the CR rate is 16 to 18%, with a median survival of 11.7 to 12.4 months.[1–3]

Given the exquisite initial sensitivity of SCLC to chemotherapy and the high rate of relapse, some studies have attempted to improve survival by increasing dose intensity. Within conventional ranges, dose intensity can be increased with the support of hematopoietic growth factors. One approach to treatment is the rapid sequencing of several active agents over a short period.[4–6] Another approach is

*From the Division of Pulmonary Medicine, Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

Manuscript received January 30, 2005; revision accepted April 26, 2005.

Correspondence to: Yoshinobu Iwasaki, MD, PhD, Division of Pulmonary Medicine, Department of Medicine, Kyoto Prefectural University of Medicine, 465 Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602, Japan; e-mail: yiwasaki@koto.kpu-m.ac.jp

the use of higher doses of chemotherapy, particularly during the first four cycles of treatment.[7,8] The dose intensity of chemotherapy has also been increased by reducing the interval between chemotherapy cycles with the use of hematopoietic growth factors.[9–12] However, whether such approaches improve survival as compared with standard therapy remains controversial.

Autologous bone marrow transplantation (ABMT) or peripheral blood stem cell transplantation (PBSCT) have been used in many studies to control the hematologic toxicity of high-dose chemotherapy, thereby permitting a further increase in dose intensity. Most studies have evaluated late intensification strategies, in which a single course of intensive chemotherapy is administered to consolidate the response to standard treatment. A combined analysis[13] revealed no apparent improvement in survival, even though the percentage of complete responders almost doubled. Another study[14] proposed that late-intensification chemotherapy might improve long-term survival in a significant proportion of complete responders with LD. To date, only one randomized, phase III trial[15] of high-dose chemotherapy followed by ABMT or PBSCT has been completed in patients with SCLC. Significant differences favoring high-dose chemotherapy were seen with respect to relapse-free survival,[15] suggesting that double-cycle, high-dose chemotherapy with ABMT or PBSCT might prolong survival by reducing the relapse rate. Multiple cycles of high-dose chemotherapy have been used as first-line therapy,[16] not for late intensification. Recently, the safety of high-dose chemotherapy has been enhanced by improvements in supportive care, including the use of hematopoietic growth factors and peripheral blood stem cells (PBSCs).

The most recent studies have evaluated ifosfamide, carboplatin, and etoposide (ifosfamide-carboplatin-etoposide [ICE]) therapy, considered to have a favorable therapeutic index.[16–19] A steep dose response coupled with synergistic antitumor activity and a favorable spectrum of nonhematopoietic toxicity makes this combination a natural candidate for high-dose therapy.[20] A phase I dose-escalation study of high-dose ICE therapy followed by ABMT or PBSCT was conducted by Fields et al[21] to determine the maximum tolerated dose. They reported that the maximum tolerated dose of ICE was 20,100 mg/m^2 of ifosfamide, 1,800 mg/m^2 of carboplatin, and 3,000 mg/m^2 of etoposide. The dose-limiting toxicities of ICE were CNS toxicity and acute renal failure. Leyvraz et al[16] showed that three cycles of high-dose ICE therapy could be safely administered as first-line therapy. In their study, three cycles of high-dose ICE therapy with 10 g/m^2 of ifosfamide, 1,200 mg/m^2 of carboplatin, and 1,200 mg/m^2 of etoposide were administered over the course of 4 days at 4-week intervals.

We treated patients with double-cycle, high-dose chemotherapy followed by PBSCT after conventional chemotherapy or chemoradiotherapy. Our main objective was to examine whether double-cycle, high-dose chemotherapy with ICE can be delivered with acceptable toxicity after conventional chemotherapy or chemoradiotherapy.

Materials and Methods

Patients

Patients with histologically confirmed SCLC of any stage were eligible for the study. Eligibility criteria included the following: (1) no previous treatment, including radiotherapy, chemotherapy, and surgery; (2) lesions that could be measured or assessed; (3) age 18 to 65 years; (4) an Eastern Cooperative Oncology Group performance status of 0 or 1; (5) a life expectancy of $\geq$ 12 weeks; (6) a blood count within the normal range, and normal cardiac, hepatic, and renal functions; and (7) $PaO_2 \geq 70$ mm Hg in a sample of arterial blood in patients with LD. As for renal function, a serum creatinine level $<$ 1.5 mg/dL and a creatinine clearance $\geq$ 60 mL/min were required at entry, immediately before the first high-dose chemotherapy, and immediately before the second high-dose chemotherapy. This study was approved by our institutional review board, and all patients provided their informed consent before enrollment.

Before study entry, all patients underwent staging investigations, including physical examination, chest radiography, CT of the chest and abdomen, brain MRI, bone scintigraphy, full blood count, electrolyte measurements, liver and renal function tests, and fiberoptic bronchoscopy with biopsy. LD was defined as tumor confined to one hemithorax with or without ipsilateral supraclavicular lymphadenopathy. All other patients were defined as having ED.

Treatment

Induction Therapy and PBSC Collection: The treatment scheme is outlined in Figure 1. Patients initially received two cycles of chemotherapy with PE at 3-week intervals. Cisplatin was administered at a dose of 80 mg/m^2 on day 1. Etoposide was administered at a dose of 100 mg/m^2 on days 1, 2, and 3. Four weeks after the first two cycles of PE, patients were administered 300 mg/m^2 of etoposide IV on days 1 to 5, followed by granulocyte colony-stimulating factor (G-CSF), 50 μg/m^2/d subcutaneously, to mobilize stem cells into the blood. PBSCs were collected by leukapheresis and cryopreserved. Collection was performed up to three times, until sufficient PBSCs were obtained to support two cycles of high-dose chemotherapy. Consecutively, two additional cycles of PE were administered at 3-week intervals.

High-Dose Therapy Followed by PBSCT: Three weeks after the last two cycles of PE, patients received high-dose ICE therapy. Ifosfamide was administered at 2.5 g/m^2/d as a 3-h IV infusion for 4 days. Carboplatin was administered at 300 mg/m^2/d as a 6-h IV infusion for 4 days. Etoposide was administered at 200 mg/m^2/d as a continuous infusion for 5 days. Mesna, 1,000 mg/m^2, was administered as a 1-h IV infusion 1 h before ifosfamide administration. Subsequently, mesna was adminis-