Double High-dose Chemotherapy Supported by Autologous Transplantation of Peripheral Blood Stem Cells for Treatment of an Elderly Patient with Small-Cell Lung Cancer

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We report a 62-year-old male with extensive disease small-cell lung cancer (SCLC) who was successfully treated with double high-dose chemotherapy supported by autologous peripheral blood stem cell transplantation (auto-PBSCT). This patient achieved a partial response with 3 cycles of induction chemotherapy. After the peripheral blood stem cell mobilization, two cycles of high-dose ICE regimen (ifosfamide 3,000 mg/m² at days 1 to 5, carboplatin 400 mg/m² at days 1, 3, 5, and etoposide 500 mg/m² at days 1, 3, 5) could be given with further regression of the tumor and acceptable toxicities. This successful case suggests the feasibility of double high-dose ICE with auto-PBSCT in elderly patients with SCLC. (Internal Medicine 38: 892-895, 1999)

Key words: double transplantation, autologous peripheral blood stem cell transplantation (auto-PBSCT)

Introduction

Lung cancer has been a primary cause of death in Japanese men since 1993, and is still increasing (1). Small-cell lung cancer (SCLC) represents 10-15% of lung cancer, and most of patients with SCLC are over 60-year-old (1). Although SCLC is highly sensitive to chemotherapy, extensive disease of SCLC (ED-SCLC) is rarely curative (2). The major cause of treatment failure is considered to be persistence or emergence of drug-resistant cells (3). Late intensification emphasized by Norton and Simon is conceptionally fascinating to overcome drug resistance (3). High-dose chemotherapy (HD-CT) with autologous transplantation of peripheral blood stem cells (auto-PBSCT) has been increasingly used in the treatment of advanced or poor prognosis malignancies (4), and use of multiple cycles of HD-CT supported by auto-PBSCT has been investigated in some selected patients (5). However, it has not been confirmed whether HD-CT with auto-PBSCT can be used safely for treatment of elderly patients with SCLC. Recently some studies indicate that prolonged disease-free survival can be expected with HD-CT in patients with limited disease of SCLC (LD-SCLC) when they are treated with HD-CT supported by bone marrow rescue (6-8). However, no survival advantage has been shown after treatment even with HD-CT in patients with ED-SCLC (9, 10). Here, we evaluated the feasibility and safety of double HD-CT in an attempt to strengthen late intensification in the treatment of ED-SCLC.

Case Report

A 62-year-old male with SCLC was referred to us in August 1995. The staging work-up disclosed the primary lesion in the right lower lobe with mediastinal lymph node swellings and multiple liver metastases; the disease was stage IV with a tumor status of T2N2M1 (Fig. 1A and 1C). An induction chemotherapy consisting of cisplatin (60 mg/m² at days 1 and 8) and irinotecan (50 mg/m² at days 1 and 8) and irinotecan (50 mg/m² at days 1 and 8) was repeated three times every 4 weeks. After this treatment, the primary lesion disappeared and liver metastases showed 92% regression; the patient achieved partial response (PR), without major organ dysfunction.

In order to increase the dose-intensity for further treatment of the residual disease, HD-CT in combination with auto-PBSCT was planned. For PBSC mobilization, high-dose etoposide (500 mg/m²) was given for 3 days, and granulocyte colony-stimulating factor (G-CSF; filgrastim, Sankyo/Kirin, Tokyo) was started at a dose of 5 μg/kg during hematological recovery from this chemotherapy. PBSC collection was per-
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Figure 1. Computed tomography revealed the primary lung tumor (C, D) and metastatic liver mass (A, B). A and C; Pretreatment. B and D; After double HD-CT with PBSC support.

formed by apheresis at days 9 and 10 of G-CSF administration using a COBE Spectra continuous blood cell separator (Cobe Laboratories, Lakewood, CA), as previously reported (11). The total number of mononuclear cells collected was $8.22 \times 10^9$ cells; CD34 positive cells and myeloid progenitor cells (CFU-GM) harvested were $1.12 \times 10^6$ and $1.68 \times 10^5$ per kilogram of the patient's body weight, respectively. These harvested cells were cryopreserved at $-80^\circ$C with a simplified method as previously reported (12).

Since a sufficient number of PBSC were harvested and adequate organ functions were confirmed, two cycles of HD-CT with auto-PBSCT were planned. For a pretransplant marrowablative regimen, a high-dose ICE regimen (13) consisting of ifosfamide (3,000 mg/m$^2$ at days 1 to 5), carboplatin (400 mg/m$^2$ at days 1, 3, and 5) and etoposide (500 mg/m$^2$ at days 1, 3, and 5) was employed. PBSC were infused 72 hours after high-dose ICE. CD34 positive cells and CFU-GM infused at the first transplant were $5.46 \times 10^6$/kg and $8.59 \times 10^5$/kg, respectively. Posttransplant hematological recovery was rapid; days to an absolute neutrophil count (ANC) >500/μl and a platelet count >50,000/μl were 9 and 27, respectively. Eight units of red blood cells and 80 units of platelets were transfused until the hematopoietic engraftment. After the second cycle of high-dose ICE, RRT was as mild as that after the first cycle; only grade 1 nausea and vomiting were noted. Febrile days with body temperature >38°C were 5 days during days 4–8 after transplantation.

Clinical courses following these two cycles of high dose ICE with auto-PBSCT are shown in Fig. 2. The final evaluation of the disease on day 21 of the second transplantation was...
CR in the primary lesion and 95% regression of the liver metastases (Fig. 1B and 1D). Finally, he received prophylactic cranial irradiation at a dose of 30 Gy just before discharge. Due to tumor progression and hepatic failure, however he died 8 months after the second transplantation, his survival period was 17 months.

**Discussion**

We described an elderly patient with ED-SCLC who was successfully treated with double PBSC-supported HD-CT with an acceptable toxicity. The survival benefit obtained by HD-CT with auto-PBSCT in SCLC patients is now under investigation. The previous trials of HD-CT with autologous bone marrow transplantation (auto-BMT) in the treatment of LD-SCLC produced a higher CR rate with no survival benefit (6, 15, 16). A randomized study comparing auto-BMT supported HD-CT with conventional-dose chemotherapy for SCLC showed longer disease-free survival in the HD-CT group, but RRT was too severe to improve the overall survival significantly (7). These disappointing results can be explained by several reasons including the advanced stage of the disease, small sample size, use of inadequate conditioning regimen, and increased transplant-related mortality. Recently Elias et al (8) demonstrated the feasibility of HD-CT with hematopoietic stem cell support using auto-PBSCT or auto-BMT in LD-SCLC, indicating prolongation of the survival in some selected patients with LD-SCLC in CR or near CR. Brugger et al (17)
reported preliminary data indicating the feasibility and prolonged disease-free survival in some patients treated with HD-CT and auto-PBSCT. However, no favorable results have been reported in ED-SCLC (9, 10). Based on these trials for SCLC, we considered that single HD-CT with PBSC support was not sufficient for the treatment of the present patient.

Many trials of double HD-CT for breast cancer, ovarian cancer and germ cell cancer, have shown the feasibility of escalation of dose-intensity (5, 18–23). However, in these trials, elderly patients were not included. For example, Ayash et al (19) treated 67 patients using double HD-CT consisting of high-dose melphalan (melphalan 140 or 180 mg/m² at day 1) with auto-PBSCT as the first intensification therapy and CTCh (cyclophosphamide 1,500 mg/m² at days 1 to 4, thiotepa 125 mg/m² at days 1 to 4, and carboplatin 200 mg/m² at days 1 to 4) with aut-BMT or auto-PBSCT as the second intensification therapy. In this trial, patient’s ages ranged from 18 to 55 years and the dose intensity of the HD-CT used was relatively low as compared with the dose intensity of the high-dose ICE given to our patient. The oldest patient that was reported to receive double HD-CT was 65 years old. But the dose intensity in that trial was also considerably low (21). The patient seems to be the first and oldest patient with SCLC treated by double myeloablative HD-CT. As a myeloablative HD-CT regimen, we used a high-dose ICE regimen based on the maximum tolerated dose in the previous dose-escalation study (13). Through we administered ifosfamide on 5 consecutive days, we divided the dose of carboplatin and etoposide on only 3 days, because we reduced the doses. Double HD-CT with PBSC support for late intensification is very attractive, if this combined therapy can eradicate the residual resistant cells in patients with ED-SCLC. However there have been no trials of double myeloablative HD-CT supported by auto-PBSCT or auto-BMT for SCLC.

Although we have had experienced only one case, and it has been successful, it is encouraging to know that an elderly patient could tolerate double myeloablative HD-CT with no fatal organ toxicities. Since the feasibility of double HD-ICE is indicated in the treatment of elderly patients with ED-SCLC, it is worth trying to evaluate the feasibility and safety of HD-CT with auto-PBSCT in a phase 2 study.

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