Intensive chemotherapy for a relapsed ALL patient who received living-donor lobar lung transplantation

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Intensive Chemotherapy for a Relapsed Acute Lymphoid Leukaemia Patient who Received Living-Donor Lobar Lung Transplantation.

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Bronchiolitis obliterans (BO) is a slowly progressive, treatment-resistant obstructive lung disease, and only lung transplantation can provide a full recovery. Since Roca et al. first reported a patient with irreversible airway obstruction, BO has been considered to be one of the symptoms of chronic GVHD after allogeneic hematopoietic stem cell transplantation (1). However, no report has yet documented intensive treatment for the patients who relapse due to underlying hematologic malignancy after receiving living-donor lobar lung transplantation (LDLLT), since LDLLT for such pulmonary complications was first reported in 1989 (2). We previously reported a patient with ALL who underwent LDLLT for progressive BO after allo-SCT (3). Unfortunately, she relapsed 66 months after the LDLLT. We herein report a patient who achieved CR by intensive chemotherapy for relapsed ALL after LDLLT.

A 17-year-old ALL female received an allogeneic BMT from her HLA-matched sibling during her 1st CR in July 1997. Neither acute nor chronic GVHD developed, and relapse was observed in October 2002. After achieving her 2nd CR by combination chemotherapy, she received high-dose cytarabine therapy following peripheral blood stem cell infusion from the same donor as provided the BM. GVHD has not developed, with no immunosuppressant use. Additional donor lymphocyte infusion (DLI) was administered on day 34. Chronic GVHD developed in the oral mucosa 2 months after DLI. A gradual progression of dry cough was observed despite the restart of CsA, and dyspnoea on exertion reached grade III on the Hugh-Jones

classification. We diagnosed the patient with progressive BO, and she received LDLLT on both sides at February 2004. Her postoperative course was uneventful and she was discharged on day 65. She has maintained CR with mild anaemia, however, palpitations and more prominent anaemia developed in August 2009. A BM smear showed 88% blasts, indicating a relapse of ALL. Renal dysfunction was observed leading to a high creatinine level with 1.2 mg/dl. Her hepatic function was normal. On arterial blood gas analysis, her pH of 7.36, pCO_2 of 35.6, and pO_2 of 92.9 were normal.

Combination chemotherapy was started based on the JALSG-ALL202 protocol, consisting of 800 mg/m^2/day of CY on day 1, 30 mg/m^2/day of DNR on days 1 to 3, 1.3 mg/m^2/day of VCR on days 1, 8, 15 and 22, and 60 mg/m^2/day of prednisolone (PSL) on days 1 to 7. It was originally intended that L-asparaginase (L-asp), 3,000 IU/m^2/day, would be administered on days 9, 11, 13, 16, 18, and 20; however, only the first 3 doses were actually given because of grade 2 liver dysfunction and grade 4 hyperglycemia, which seemed to be adverse events of the L-asp, graded by common terminology criteria for adverse events (CTCAE) version 3.0 of National Cancer Institute (USA). G-CSF stimulation factor was administered for myelosuppression on days 11 to 25. A skin rash (grade 3) and syndrome of inappropriate antidiuretic hormone secretion (grade 3) responsive to supportive therapy developed on day 25. She achieved a 3rd CR on day 37. Hence, the cumulative dose of anthracycline antineoplastic drugs reached 400 mg/m^2 at this point (the dose of

anthracycline was calculated as the equivalent dose of native doxorubicin) (4), subsequent administration of anthracycline was discontinued to avoid severe cardiac complications (4, 5). The first consolidation chemotherapy consisted of 2 g/m^2/day of CY on days 1 to 3, 100 mg/m^2/day of etoposide on days 1 to 3 and 40 mg/body/day of dexamethazone (Dexa) on days 1 to 3, and intrathecal injection of MTX and Dexa was subsequently performed. Mild subileus was complicated during the course. Renal dysfunction was temporarily exacerbated after prophylactic itraconazole treatment, thus leading to transient high blood levels of tacrolimus, but the creatinine levels improved to the levels before starting chemotherapy. The second consolidation therapy consisted of 1.3 mg/m^2/day of VCR on day 1, 500 mg/m^2/day of MTX with leucovorin rescue on day 1, and 25 mg/m^2/day of 6-mercaptopurine (6-MP) on days 1 to 21, and was started on day 34 after the 1st consolidation therapy; but recurrence of skin rash and subileus were observed after this course. Hence, the 2nd VCR and MTX administration on day 15 was stopped. A tremor-like involuntary movement temporarily developed on the 5th day after the 1st consolidation therapy and the 3rd day after 2nd consolidation therapy. An intrathecal injection was performed in day 1, respectively, and no abnormality was seen on electrolyte or radiological examinations, and these involuntary movements were diagnosed to be drug-induced leukoencephalopathy. Maintenance therapy consisting of 60 mg/m^2/day of PSL for 5 days and 60 mg/m^2/day of 6-MP for 14 days was scheduled every month, and the

patient was discharged on day 143 after one dose of maintenance therapy. She continues to take PSL and 6-MP monthly as an outpatient, and has remained in her 3rd CR for 12 months with a good performance status (PS).

No report has so far been published regarding chemotherapy for LDLLT patients with malignancy. In such cases, the development of critical adverse events caused by decreased pulmonary reserve and the effects of immunosuppressive agents are of deep concern. In our case, various complications were observed, however, the symptoms were tolerated, and her respiratory function remained stable during the treatment (Table 1). Figure 1 shows the time course of the correlation between respiratory function and PS since the patient's initial diagnosis; worsening of her PS and development of BO was observed simultaneously. Her PS recovered after LDLLT, when her respiratory function became stable. Despite the PS worsening for the short-term during the chemotherapy, her PS eventually recovered and returned to her normal lifestyle. No contributing lung complications leading to an aggravation of the respiratory function were observed.

Most physicians might hesitate to perform intensive chemotherapy for patients who have decreased organ reserve and are taking immunosuppressants. We believe this case indicates that chemotherapy should be considered even for such patients, and that physician should not draw quick any conclusions regarding the use of only palliative care, because they could also have a good outcome with chemotherapy.

Conflict of interest

The authors declare no conflict of interest.

Figure Legend

Figure 1. Changes in Respiratory Function and Performance Status. The patient's forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and performance status (PS) was decreased just before she was diagnosed with bronchiolitis obliterans (BO). Her PS fully recovered, and FVC and FEV1 were partially recovered after living-donor lobar lung transplantation (LDLLT), and this recovery lasted until her 3rd relapse of acute lymphoid leukemia. Her PS was then transiently decreased during the chemotherapy, but her respiratory function remained stable. The performance status was evaluated by the ECOG criteria(6).

References

1. Roca J, Granena A, Rodriguez-Roisin R, Alvarez P, Agusti-Vidal A, Rozman C. Fatal airway disease in an adult with chronic graft-versus-host disease. *Thorax* 1982; **37**(1)**:** 77-8.

2. Clark JG, Crawford SW, Madtes DK, Sullivan KM. Obstructive lung disease after allogeneic marrow transplantation. Clinical presentation and course. *Ann Intern Med* 1989; **111**(5)**:** 368-76.

3. Okumura H, Ohtake S, Ontachi Y, Ozaki J, Shimadoi S, Waseda Y *et al.* Living-donor lobar lung transplantation for broncho-bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation: does bronchiolitis obliterans recur in transplanted lungs? *Int J Hematol* 2007; **86**(4)**:** 369-73.

4. Sakata-Yanagimoto M, Kanda Y, Nakagawa M, Asano-Mori Y, Kandabashi K, Izutsu K *et al.* Predictors for severe cardiac complications after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004; **33**(10)**:** 1043-7.

5. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1998; **339**(13)**:** 900-5.

6. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**(6)**:** 649-55.

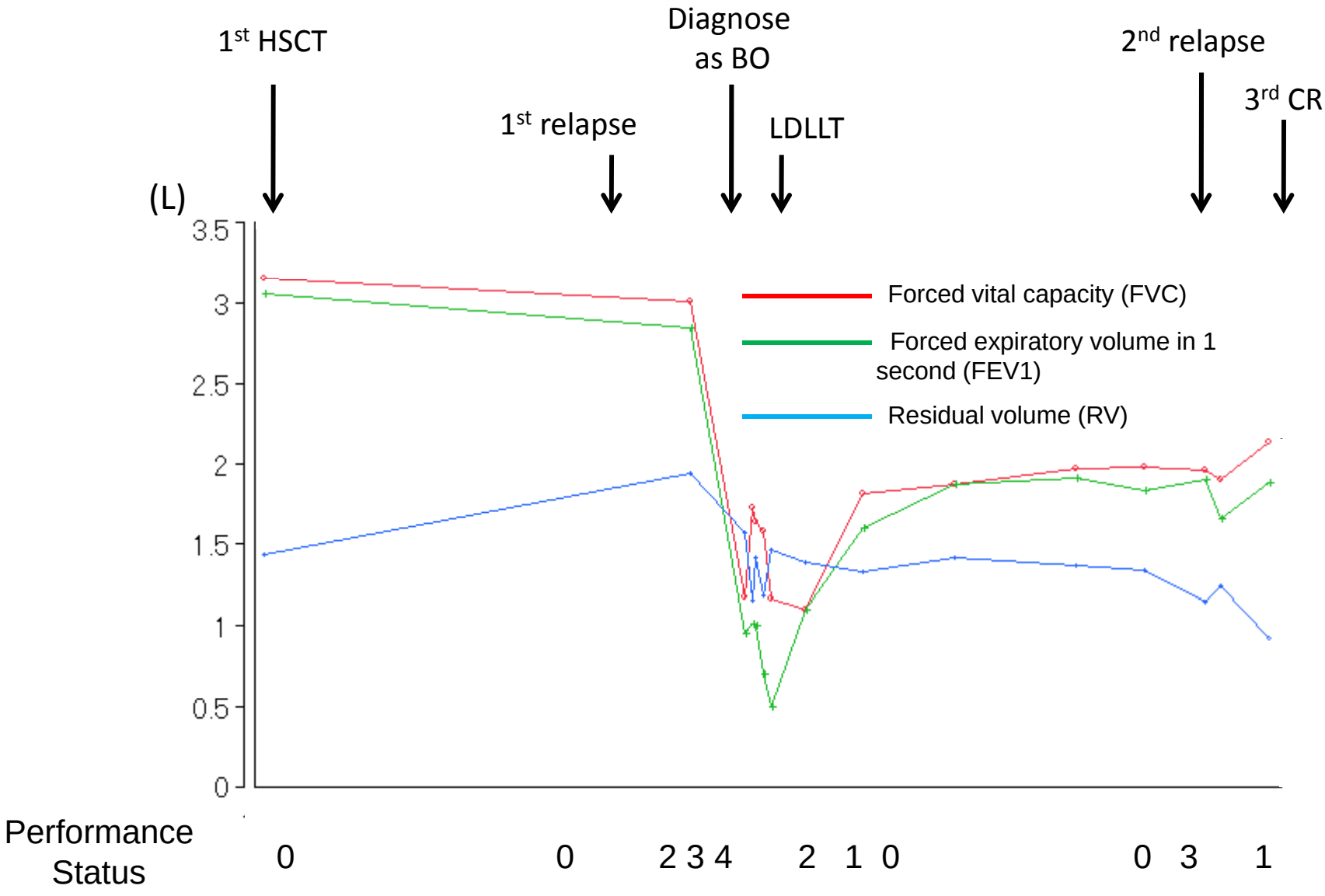

Figure 1. Changes in Respiratory Functions and Performance Status

Table 1. Changes of respiratory function since LDLLT

		Post LDLLT	Before Remission-Induction Therapy	After Consolidation Therapy
Forced Vital Capacity (FVC)	(L)	1.98	1.90	2.13
predicted value	(%)	67.8	67.1	74.7
Forced Expiratory Volume in 1 Second (FEV1.0)	(L)	1.83	1.66	1.88
predicted value	(%)	64.4	61.9	69.4
Forced Expiratory Volume in 1 Second as Percent of FVC (FEV1.0%)	(%)	92.4	87.4	88.3
predicted value	(%)	109.3	103.7	105.1
Maximal Mid-expiratory Flow (MMF)	(L/sec)	1.93	1.60	1.87

Abbreviation; LDLLT, living-donor lobar lung transplantation.