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A Retrospective Analysis of Allogeneic Hematopoietic Stem Cell Transplantation for Adult T Cell Leukemia/Lymphoma (ATL): Clinical Impact of Graft-versus-Leukemia/Lymphoma Effect

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ABSTRACT

Adult T cell leukemia/lymphoma (ATL) is a highly aggressive T cell malignancy, and has a poor prognosis. Recently, allogeneic-hematopoietic stem cell transplantation (allo-HSCT) has been suggested to improve the outcome. We retrospectively analyzed 15 patients with ATL who had received allo-HSCT in 2 institutions in Hokkaido, Japan. The median age of the patients was 57 years. The estimated 3-year overall survival (OS) and progression-free survival (PFS) rates were 73.3% and 66.7%, respectively. Calcineurin inhibitor dosage was reduced and administration was discontinued abruptly in 6 of the 15 patients for disease control; as a result, 4 (66.7%) of the 6 patients achieved complete response (CR) or partial response. Therefore, a graft-versus-leukemia/lymphoma (GVL) effect might be induced by discontinuation of immunosuppression. Thirteen of the 15 patients were followed up by monitoring HTLV-1 proviral DNA levels. In 10 of the 11 patients with positive HTLV-1 proviral DNA before allo-HSCT, HTLV-1 proviral DNA became undetectable at least once after allo-HSCT, and only 1 of the 5 patients in whom HTLV-1 proviral DNA became detectable after allo-HSCT relapsed. Compared to the results of past studies, these results show that allo-HSCT greatly improved the prognosis of ATL and suggest a contribution of the induction of a GVL effect.

KEY WORDS

Adult T cell leukemia/lymphoma • Human T cell lymphotropic virus type 1 • Allogeneic stem cell transplantation • HTLV-1 proviral DNA • GVL effect

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is a highly aggressive T cell malignancy associated with infection of a retrovirus, human T cell lymphotropic virus type 1 (HTLV-1) [1-4]. Acute and lymphoma types of ATL have a particularly poor prognosis because of resistance to conventional chemotherapy or high-dose chemotherapy at an early stage during its clinical course. The median survival periods for patients with these subtypes of ATL who have received chemotherapy are 3 to 13 months [5-8].

Successful allogeneic-hematopoietic stem cell transplantation (allo-HSCT) has recently been reported, and several groups have reported encouraging

results of allo-HSCT for ATL. A graft-versus-leukemia/lymphoma (GVL) effect has also been suggested to improve treatment outcomes.

We retrospectively analyzed 15 patients with ATL who had received allo-HSCT in the Hokkaido University Hospital and the Sapporo Hokuyu Hospital. Compared to results of past studies, our results more strongly suggest that allo-HSCT improves the outcome for ATL, and that a GVL effect improves the clinical outcome after allo-HSCT.

PATIENTS AND METHODS

Diagnosis and Classification of clinical Subtypes of ATL

In all cases, the diagnosis of ATL was based on clinical features, immunophenotype, presence of anti-HTLV-1 antibody, and clonal integration of HTLV-1 proviral DNA. Clinical subtypes of ATL were classified according to the criteria of the Japanese Lymphoma Study Group [9].

Response to Treatment

The response criteria were defined as follows [5]: complete response (CR, resolution of all malignant disease for 4 weeks or more); partial remission (PR, reduction in measurable indices lasting 4 weeks or more, without the development of new lesions or disease progression); and progressive disease (PD, increase in measurable disease or in the number of circulating leukemic cells by 25% or more).

Patients' Characteristics

Fifteen patients with ATL (acute-type, n = 6; lymphoma-type, n = 8; chronic-type, n = 1) received allo-HSCT at the Hokkaido University Hospital and the Sapporo Hokuyu Hospital between 2000 and 2007. These hospitals are located in Hokkaido, an area of Japan in which there is a small number of HTLV-1 infection cases compared to the number of cases in the Shikoku or Kyushu districts of Japan. The patient with chronic type of ATL received allo-HSCT because of poor disease control and the existence of an appropriate HLA-identical sibling donor.

Clinical characteristics of the ATL patients are shown in Tables 1 and 2. The median age at the time of diagnosis was 57 years (range: 41-66 years). Disease statuses at SCT were CR in 9 patients (molecular CR in 1 patient), PR in 5 patients, and PD in 1 patient. Eight patients received stem cells from bone marrow (BM), 4 patients received stem cells from peripheral blood (PB), and 3 patients received stem cells from BM and PB. Ten patients underwent transplantation from HLA-identical siblings, 2 donors having anti-HTLV-1 antibodies, and 5 patients underwent transplantation from unrelated HLA-identical donors.

Preconditioning Regimens and Graft-versus-Host Disease (GVHD) Prophylaxis

Five patients received a conventional regimen (etoposide + cyclophosphamide [Cy] + total-body irradiation [TBI]), and 10 patients received a reduced-intensity (RIC) regimen (fludarabine [Flu] + busulphan [Bu] ± TBI for 5 patients and Flu + melphalan ± TBI for 5 patients). GVHD prophylaxis consisted of treatment with cyclosporine (CsA) or tacrolimus (FK) and short-term methotrexate (sMTX): CsA + sMTX in 11 patients and FK + sMTX in 4 patients (Table 2).

Measurement of HTLV-1 Proviral DNA

HTLV-1 proviral DNA was measured in mononuclear cells of PB or BM before and after allo-HSCT by Southern blot hybridization, dot blot qualitative analysis using polymerase chain reaction (PCR) amplification of the HTLV-1 pX gene and gag gene, and quantitative real-time PCR amplification of HTLV-1 tax gene, according to the recommendations of the manufacture's (SRL, Inc. and Mitsubishi Chemical Medience Corporation). The quantitative real-time PCR method has been previously described [10].

Statistical Analysis

Overall survival (OS) and progression-free survival (PFS) were analyzed according to the method of Kaplan and Meier. OS was calculated from the day of allo-HSCT until death or last-follow up, and PFS was calculated until disease progression, death, or last follow-up.

RESULTS

Engraftment

All patients tolerated the conditioning regimen and achieved neutrophil recovery ($0.5 \times 10^4/\mu L$) at a median of 17 days (range: 14-20 days) (Table 3), and 13 of the 15 patients achieved platelet recovery exceeding $5.0 \times 10^4/\mu L$ at a median of 29 days (range: 14-46 days).

GVHD

Acute GVHD (aGVHD) developed in 8 (53.3%) of the 15 patients: grade I GVHD in 1 patient, grade II in 5 patients and grade III in 2 patients. Chronic GVHD (cGVHD) developed in 10 (76.9%) of 13 patients followed up over 100 days from transplantation, with limited disease in 3 patients and extensive disease in 7 patients (Table 3). Two patients developed grade III aGVHD after reduction in the dose of and abrupt discontinuation of administration of a calcineurin inhibitor for induction of a GV-ATL effect, and 1 patient (Case 6) also developed severe cGVHD after discontinuation of the immunosuppression.

Table 1. *Patients characteristics*

	Age/Sex	Subtype	WBC (/μL) (Abnormal Lymphocyte(/μL))	LDH(IU/L)	Organ Involvement	Induction Therapy
Case 1	41/F	Acute	27,300 (18,837)	NA	Skin	mNLG-2
Case 2	44/M	Acute	331,000 (304,520)	1611	Liver	CHOP-V-MMV
Case 3	46/F	Chronic	10,900 (0)	245	Skin	PUVA+DCF
Case 4	47/F	Lymphoma	2500 (0)	340	—	CHOP-E
Case 5	49/F	Lymphoma	20,500 (820)	603	Spleen	CHOP→VCAP/AMP/VECP
Case 6	53/F	Lymphoma	6800 (0)	326	—	DCF→CHOP
Case 7	56/F	Lymphoma	5100 (0)	558	—	VCAP/AMP/VECP
Case 8	57/F	Lymphoma	9430 (0)	165	GI tract	VCAP/AMP/VECP
Case 9	58/M	Lymphoma	8050 (0)	208	—	CHOP→VCAP/AMP/VECP
Case 10	60/F	Acute	17,800 (8188)	290	Spleen	VCAP/AMP/VECP
Case 11	60/F	Lymphoma	NA (12,000)	593	—	VCAP/AMP/VECP
Case 12	61/F	Lymphoma	5000 (115)	363	—	CHOP
Case 13	62/F	Acute	39,200 (10,976)	1216	Liver, Skin	VEPA
Case 14	64/F	Acute	15,840 (5544)	418	—	VCAP/AMP/VECP
Case 15	66/M	Acute	26,000 (13,780)	595	Liver, Skin, PE	VCAP/AMP/VECP

GI tract indicates gastrointestinal tract; PE, pleural effusion; mNLG-2, cyclophosphamide, adriamycin, vincristine prednisolone, tetrahydropyranyl adriamycin, ranimustine, vindesine, etoposide, carboplatin; CHOP-V-MMV, cyclophosphamide doxorubicin, vincristine, prednisolone, etoposide, vindesine, ranimustine, mitoxantrone; PUVA, psoralen and ultraviolet light; DCF, deoxycoformycin; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; VCAP, vincristine, adriamycin cyclophosphamide, prednisolone; AMP, adriamycin, ranimustine, prednisolone; VECP, vindesine, etoposide, carboplatin prednisolone; VEPA, vincristine, cyclophosphamide, prednisolone, doxorubicin.

Induction of a GVL Effect

A calcineurin inhibitor dose was reduced and administration was abruptly discontinued in 6 of the 15 patients for induction of a GVL effect because of relapse, regrowth of residual disease, remaining ATLL cells, or remaining recipient-type cells in chimerism analysis. As a result, 3 patients (Cases 2, 7, and 13) achieved CR, 1 patient (Case 10) achieved PR, and 2 patients (Cases 5 and 8) had PD. However, 2 of the 3 patients who achieved CR developed grade III aGVHD and 1 of the 3 patients developed lung cGVHD for which mechanical ventilation was temporarily needed.

Survival, Relapse (or Disease Progression), and Treatment-Related Mortality (TRM)

The median follow-up period after transplantation was 35.5 months (range: 1.5-86.0 months) and the median PFS period after transplantation was 35.5 months (range: 0.4-86.0 months). The estimated 3-year OS and PFS rates were 73.3% and 66.7%, respectively (Figure 1). Four of the 5 patients who received CST are alive and 1 patient (Case 5) died of relapse 477 days after transplantation. Seven of the 10 patients who received RIST are alive. One patient (Case 8) died of disease progression 45 days after transplantation, and 2 patients (Cases 9 and 15)

Table 2. *Transplant characteristics*

	Time from Diagnosis to SCT(Days)	Disease Status	Donor	Stem Cell Source	Conditioning Regimen	GVHD Prophylaxis
Case 1	150	CR	Related	BM+PB	VP-16+Cy+TBI	CsA+sMTX
Case 2	215	PR	Related	BM	VP-16+Cy+TBI	CsA+sMTX
Case 3	825	PR	Related	BM	VP-16+Cy+TBI	CsA+sMTX
Case 4	150	CR	Related	BM+PB	VP-16+Cy+TBI	CsA+sMTX
Case 5	425	PR	Unrelated	BM	VP-16+Cy+TBI	FK+sMTX
Case 6	1275	CR	Unrelated	BM	Flu+L-PAM+TBI	FK+sMTX
Case 7	680	PR	Unrelated	BM	Flu+BU+TBI	CsA+sMTX
Case 8	153	PD	Related	BM	Flu+BU+TBI	CsA+sMTX
Case 9	196	CR	Related	PB	Flu+L-PAM	CsA+sMTX
Case 10	157	CR	Unrelated	BM	Flu+BU+TBI	FK+sMTX
Case 11	232	PR	Related (HTLV-1(+))	PB	Flu+L-PAM	CsA+sMTX
Case 12	371	CR	Related	BM+PB	Flu+L-PAM	CsA+sMTX
Case 13	140	CR	Related	PB	Flu+BU	CsA+sMTX
Case 14	297	CR	Unrelated	BM	Flu+BU+TBI	FK+sMTX
Case 15	127	CR	Related (HTLV-1(+))	PB	Flu+L-PAM	CsA+sMTX

VP-16 indicates etoposide; Cy, cyclophosphamide; TBI, total body irradiation; Flu, fludarabine; L-PAM, melphalan; BU, busulfan; CsA, cyclosporine; FK, tacrolomus; sMTX, short-term methotrexate.

Table 3. *Transplant outcomes*

	Engraftment (Day) Neutrophil/Platelet	aGVHD (Day/Grade)	aGVHD (Day/Type)	Outcome	Cause of Death	Follow-up Time (Month)
Case 1	18/46	None	120/Extensive	CR	Alive	79.0+
Case 2	15/24	31/?	351/Extensive	CR(after d/c CI)	Alive	61.7+
Case 3	16/26	57/?	365/Extensive	CR	Alive	69.1+
Case 4	17/29	26/?	252/Limited	CR	Alive	86.0+
Case 5	15/27	26/?	160/Limited	Dead, d477	Relapse	16.0
Case 6	17/26	None	None	CR	Alive	37.0+
Case 7	14/29	None	None	CR (complete chimera after reducing CI)	Alive	45.3+
Case 8	16/24	8/?	Not evaluable	Dead, d45	Disease progression	1.5
Case 9	14/33	None	None	Dead, d296	TTP	9.7
Case 10	17/30	69/?	210/Extensive	LN relapse,d192 (PR after d/c CI)	Alive	21.2+
Case 11	20/-	None	142/Extensive	CR	Alive	35.5+
Case 12	16/26	None	132/Extensive	CR	Alive	31.0+
Case 13	16/14	29/?	69/Extensive	CR (complete chimera after d/c CI)	Alive	58.9+
Case 14	16/31	None	80/Limited	CR	Alive	4.6+
Case 15	19/-	17/?	Not evaluable	Dead, day46	Bacterial pneumonia	1.5

CI indicates calcineurin inhibitor; TTP, thrombotic thrombocytopenic purpura.

died of TRM because of allo-SCT-related thrombotic thrombocytopenic purpura (TTP) and bacterial pneumonia (Table 3). In 2 patients whose donors had anti-HTLV-1 antibodies, 1 patient (Case 11) is alive and has achieved CR (with negative HTLV-1 proviral DNA), and the other patient (Case 15) died of TRM.

Also, none of the patients were treated with antiretroviral agents after HSCT.

Clinical Course of HTLV-1 Proviral DNA

Thirteen of the 15 patients were followed up by monitoring HTLV-1 proviral DNA levels before and after allo-HSCT (Figure 2). In 10 of the 11 patients with positive HTLV-1 proviral DNA before allo-HSCT, HTLV-1 proviral DNA became undetectable more than 1 time after allo-HSCT. (One patient [Case 1] was followed up in another hospital, so the last day for data of HTLV-1 proviral DNA was day 120, and was positive by dot blot qualitative analysis using PCR amplification of the HTLV-1 gag gene.) Although HTLV-1 proviral DNA became detectable in 5 patients again (Cases 4, 5, 7, 10, and 13), 1 of those patients (Case 5) relapsed with leukemia 6 months after allo-HSCT. Case 10 also relapsed in lymph nodes but remained in CR in peripheral blood and bone marrow at that time. In 2 patients with negative HTLV-1 proviral DNA by Southern blot hybridization before allo-HSCT, 1 patient (Case 9) died of TRM and 1 patient (Case 11) is alive, and the status of HTLV-1 proviral DNA remained undetectable in both of those patients.

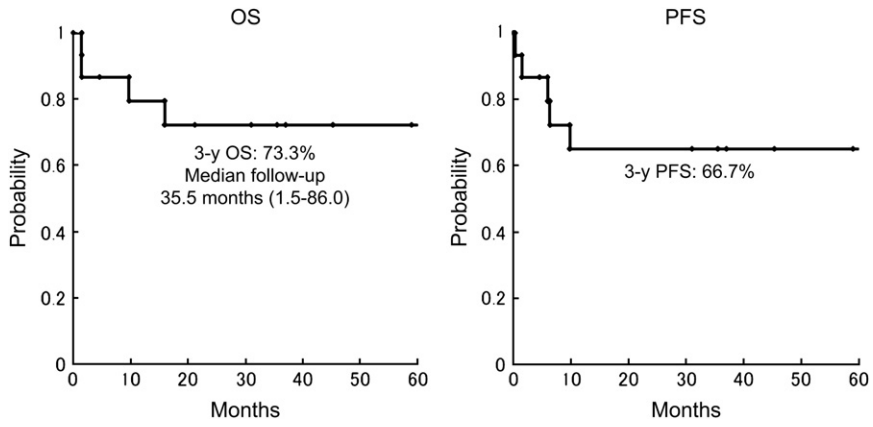

Figure 1. Kaplan-Meier plot of OS and PFS following allogeneic stem cell transplantation for ATL.

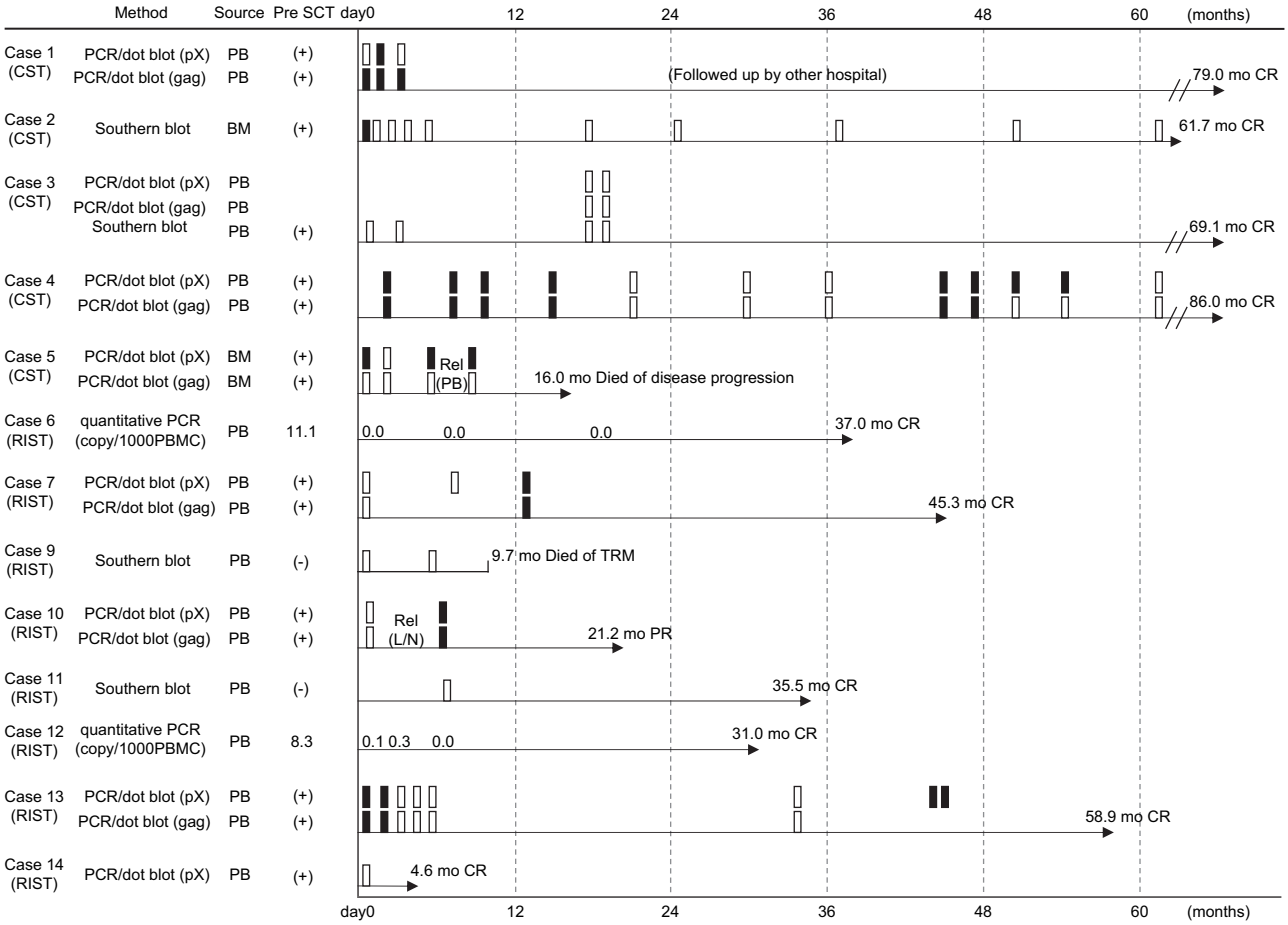

Figure 2. Transition of HTLV-1 proviral DNA before and after allo-HSCT (open squares: negative results, closed squares: positive results).

DISCUSSION

ATL is a highly aggressive hematologic malignancy, and its prognosis is poor because ATL cells are resistant to chemotherapy at an early stage. Cases of treatment with allo-HSCT have been reported since 1987 [11], and since the report of Utsunomiya et al. in 2001 [12], results of several retrospective analyses and a phase I clinical trial of allo-HSCT for ATL have been reported in Japan [13-17]. Survival periods of patients in those studies ranged from 33.3% to 60% for OS and from 20% to 64% for TRM. In our retrospective analysis, 3-year OS was 73.3%, 3-year PFS was 66.7%, and TRM was 20%. These results of allo-HSCT with ATL are much better than those of past studies. Disease progression occurred in only 2 patients (13.3%) after allo-HSCT in this study. The background of this outcome is considered to be that there was only 1 patient with PD before allo-HSCT and better disease control by the induction chemotherapy was obtained in many cases, although these were not greatly different from those in past studies. Also, regarding the lower TRM rate, there was not a great difference in GVHD prophylaxis compared to that in past studies, and special treatment of infection was not done compared to other hematologic malignancies in our hospital. As mentioned above, this study was carried out in Hokkaido, an area of Japan in which there is a small number of HTLV-1 infection cases, and past studies were carried out in Kyushu and Shikoku, areas in which HTLV-1 infection is endemic. Some studies have shown several subtypes of HTLV-1 provirus, and the significance of these subtypes in oncogenesis of ATL has been suggested [18-22]. Although this study was a retrospective analysis and we could not investigate the subtypes of HTLV-1 provirus, 1 reason for the good outcome in this study might be related to the difference in subtypes of ATL. Further studies are needed to clarify the relationship between subtypes of HTLV-1 provirus and prognosis of ATL.

Another reason might be the induction of a GVL effect by reducing the dose of and abrupt discontinuation of administration of a calcineurin inhibitor. A relationship between GVHD and GVL effect has been reported in acute lymphoblastic leukemia (ALL) [23,24]. In ATL, there have also been some reports

about the efficacy of abrupt discontinuation of immunosuppression for a GVL effect [25-27], and the generation of cytotoxic T lymphocytes against some epitopes of ATL cells might be induced [28-30]. In our study, 4 (66.7%) of the 6 patients in whom the dose of a calcineurin inhibitor was reduced and administration was abruptly discontinued achieved CR or PR, suggesting that these are effective for induction of a GVL effect. However, discontinuation of the administration of a calcineurin inhibitor was not effective for 2 patients (Cases 5 and 8) in whom disease progression developed rapidly after allo-HSCT. Thus, it is thought that a GVL effect induced by abrupt discontinuation of immunosuppression may not be sufficient for disease control at the stage of aggressive disease progression. It is possible that the magnitude of a GVL effect varies with the individual, but this is not clear in the present study. Further studies are needed to clarify the mechanism of a GVL effect. On the other hand, most of the cases in which disease control was achieved by abrupt discontinuation of administration of a calcineurin inhibitor developed severe GVHD, suggesting that a balance between GVHD and GVL effect is a critical point in clinical management. However, immunosuppression (calcineurin inhibitor and/or steroid) was restarted in all cases with severe GVHD. Because no cases showed regrowth of ATL or reappearance of recipient-type cells in chimerism analysis for the restart of immunosuppression, a GVL effect induced by abrupt discontinuation of calcineurin inhibitor may continue for a long time even after the restart of immunosuppression.

In this study, HTLV-1 proviral DNA became undetectable more than 1 time after allo-HSCT in all patients with positive HTLV-1 proviral DNA before allo-HSCT. However, in 5 patients, HTLV-1 proviral DNA became detectable again, and only 1 patient relapsed. Because complete chimerism was maintained in peripheral blood in the other 4 patients, donor-derived cells appeared to be infected with HTLV-1 in the host after allo-HSCT according to the results of a past study [31]. Further studies are needed to clarify the association between relapse and reappearance of HTLV-1 proviral DNA after allo-HSCT.

The risk factors before allo-HSCT, particularly the disease status in allo-HSCT for ATL, are still unclear. In this study, the patient who had PD before allo-HSCT developed disease progression at an early stage after allo-HSCT. On the other hand, in the patients who had been in PR before allo-HSCT, only 1 patient relapsed after allo-HSCT and the other 4 patients have been in CR, an outcome that is not inferior to the outcome of patients who had been in CR before allo-HSCT. Further studies are needed to establish the of risk classification in allo-HSCT with ATL.

REFERENCES

1. Uchiyama T, Yodoi J, Sagawa K, et al. Adult T-cell leukemia: clinical and hematologic features of 16 cases. *Blood*. 1977;50: 481-492.
2. Poiesz BJ, Ruscetti FW, Gazdar AF, et al. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci USA*. 1980;77:7415-7419.
3. Hinuma Y, Nagata K, Hanaoka M, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc Natl Acad Sci USA*. 1981;78:6476-6480.
4. Yoshida M, Miyoshi I, Hinuma Y. A retrovirus from human leukemia cell lines: its isolation, characterization, and implication in human adult T-cell leukemia (ATL). *Proc Natl Acad Sci USA*. 1982;79:2031-2035.
5. Gill PS, Harrington W Jr., Kaplan MH, et al. Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. *N Engl J Med*. 1995;332:1744-1748.
6. Taguchi H, Kinoshita KI, Takatsuki K, et al. An intensive chemotherapy of adult T-cell leukemia/lymphoma: CHOP followed by etoposide, vindesine, ranimustine, and mitoxantrone with granulocyte colony-stimulating factor support. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;12:182-186.
7. Yamada Y, Tomonaga M, Fukuda H, et al. A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukaemia-lymphoma: Japan Clinical Oncology Group Study 9303. *Br J Haematol*. 2001;113:375-382.
8. Tsukasaki K, Utsunomiya A, Fukuda H, et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. *J Clin Oncol*. 2007;25:5458-5464.
9. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). *Br J Haematol*. 1991; 79:428-437.
10. Miyazato P, Yasunaga J, Taniguchi Y, et al. De novo human T-cell leukemia virus type 1 infection of human lymphocytes in NOD-SCID, common gamma-chain knockout mice. *J Virol*. 2006;80:10683-10691.
11. Sobue R, Yamauchim T, Miyamura K, et al. Treatment of adult T cell leukemia with mega-dose cyclophosphamide and total body irradiation followed by allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1987;2:441-444.
12. Utsunomiya A, Miyazaki Y, Takatsuka Y, et al. Improved outcome of adult T cell leukemia/lymphoma with allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;27:15-20.
13. Kami M, Hamaki T, Miyakoshi S, et al. Allogeneic haematopoietic stem cell transplantation for the treatment of adult T-cell leukaemia/lymphoma. *Br J Haematol*. 2003;120:304-309.
14. Fukushima T, Miyazaki Y, Honda S, et al. Allogeneic hematopoietic stem cell transplantation provides sustained long-term survival for patients with adult T-cell leukemia/lymphoma. *Leukemia*. 2005;19:829-834.
15. Okamura J, Utsunomiya A, Tanosaki R, et al. Allogeneic stem-cell transplantation with reduced conditioning intensity as a novel immunotherapy and antiviral therapy for adult T-cell leukemia/lymphoma. *Blood*. 2005;105:4143-4145.
16. Nakase K, Hara M, Kozuka T, et al. Bone marrow transplantation from unrelated donors for patients with adult T-cell leukaemia/lymphoma. *Bone Marrow Transplant*. 2006;37:41-44.

17. Kato K, Kanda Y, Eto T, et al. Allogeneic bone marrow transplantation from unrelated human T-cell leukemia virus-I-negative donors for adult T-cell leukemia/lymphoma: retrospective analysis of data from the Japan Marrow Donor Program. *Biol Blood Marrow Transplant*. 2007;13:90-99.
18. Tamiya S, Matsuoka M, Etoh K, et al. Two types of defective human T-lymphotropic virus type I provirus in adult T-cell leukemia. *Blood*. 1996;88:3065-3073.
19. Koiwa T, Hamano-Usami A, Ishida T, et al. 5'-Long terminal repeat-selective CpG methylation of latent human T-cell leukemia virus type 1 provirus in vitro and in vivo. *J Virol*. 2002;76:9389-9397.
20. Takeda S, Maeda M, Morikawa S, et al. Genetic and epigenetic inactivation of tax gene in adult T-cell leukemia cells. *Int J Cancer*. 2004;109:559-567.
21. Taniguchi Y, Nosaka K, Yasunaga J, et al. Silencing of human T-cell leukemia virus type I gene transcription by epigenetic mechanisms. *Retrovirology*. 2005;2:64.
22. Miyazaki M, Yasunaga J, Taniguchi Y, et al. Preferential selection of human T-cell leukemia virus type 1 provirus lacking the 5' long terminal repeat during oncogenesis. *J Virol*. 2007;81:5714-5723.
23. Weiden PL, Sullivan KM, Flournoy N, Storb R, Thomas ED. Antileukemic effect of chronic graft-versus-host disease: contribution to improved survival after allogeneic marrow transplantation. *N Engl J Med*. 1981;304:1529-1533.
24. Passweg JR, Tiberghien P, Cahn JY, et al. Graft-versus-leukemia effects in T lineage and B lineage acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1998;21:153-158.
25. Ohguchi H, Sai T, Hamazaki Y, et al. Cyclosporin A withdrawal causes spontaneous remission of recurrent subcutaneous tumors after allogeneic peripheral blood stem cell transplantation for adult T-cell leukemia/lymphoma. *Rinsho Ketsueki*. 2003;44:102-107.
26. Ota K, Hashino S, Shimizu K, et al. Eradication of adult T-cell leukemia cells and maintenance of remission by the graft-versus-leukemia effect after allogeneic bone marrow transplantation. *Rinsho Ketsueki*. 2004;45:1044-1047.
27. Hara S, Yokote T, Akioka T, et al. Graft-versus-ATLL effect induced by abrupt discontinuation of immunosuppression following allogeneic bone marrow transplantation. *Gan To Kagaku Ryoho*. 2005;32:867-871.
28. Harashima N, Kurihara K, Utsunomiya A, et al. Graft-versus-Tax response in adult T-cell leukemia patients after hematopoietic stem cell transplantation. *Cancer Res*. 2004;64:391-399.
29. Harashima N, Tanosaki R, Shimizu Y, et al. Identification of two new HLA-A*1101-restricted tax epitopes recognized by cytotoxic T lymphocytes in an adult T-cell leukemia patient after hematopoietic stem cell transplantation. *J Virol*. 2005;79:10088-10092.
30. Hishizawa M, Imada K, Sakai T, et al. Antibody responses associated with the graft-versus-leukemia effect in adult T-cell leukemia. *Int J Hematol*. 2006;83:351-355.
31. Yamasaki R, Miyazaki Y, Moriuchi Y, et al. Small number of HTLV-1-positive cells frequently remains during complete remission after allogeneic hematopoietic stem cell transplantation that are heterogeneous in origin among cases with adult T-cell leukemia/lymphoma. *Leukemia*. 2007;21:1212-1217.