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Review Article

Recent advances in the treatment of adult T-cell leukemia-lymphomas

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Key words

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Recent advances in treatment for adult T-cell leukemia-lymphoma (ATL) are reviewed herein. It is currently possible to select a therapeutic strategy for ATL and predict prognosis by classification of patients by clinical subtypes and clinicopathological factors. Although the overall survival (OS) of patients with ATL has increased marginally because of advances in chemotherapy, further prolongation of survival might be difficult with conventional chemotherapy alone. Promising results have been reported for antiviral therapy using zidovudine and interferon-α, and, indeed, antiviral therapy is currently the standard treatment for patients with ATL in western countries. Remarkably, the 5-year OS rates are 100% for both the smoldering-type and chronic-type ATL. Recently, treatments for ATL have included allogeneic hematopoietic stem cell transplantation and molecular targeted therapies. Furthermore, the anti-CCR4 monoclonal antibody mogamulizumab has been shown to have marked cytotoxic effects on ATL cells, especially in the leukemic type of ATL. In the lymphoma type of ATL, the response rate may be improved by combining mogamulizumab with chemotherapy. It should be recognized that prevention of infection from carriers of human T-cell leukemia virus type-I and transfer of the virus from mother to infant are crucial issues for the eradication of ATL.

Adult T-cell leukemia-lymphoma (ATL) is a mature T-cell neoplasm caused by human T-cell leukemia virus type-I (HTLV-1).[1] Following the initial report by Uchiyama *et al.*,[2] many key discoveries concerning the mechanism of leukemogenesis of ATL have been made in association with the HTLV-1 *tax* and HTLV-1 *basic leucine zipper factor* genes.[3,4] Several clinical manifestations of ATL are known and may be classified into four clinical subtypes based on the presence of organ involvement and the results of blood workup.[5] This classification is currently used as the basis for therapeutic strategies.

Therapeutic interventions, including intensive chemotherapy for aggressive ATL, are not associated with satisfactory outcomes, mainly because ATL cells are often resistant to chemotherapeutic agents;[6] moreover, patients with ATL frequently suffer from a number of opportunistic infections.[5] We reported for the first time that allogeneic hematopoietic stem cell transplantation (allo-HSCT) improved overall survival (OS) in ATL patients.[7]

In Europe and USA, antiviral therapy has been frequently applied for ATL patients since the therapeutic efficacy of zidovudine (AZT) and interferon-α (IFN) has been demostrated.[8,9] More recently, the mechanism of action of AZT combined with IFN (AZT/IFN) has been partially elucidated.[10] Antiviral therapy has received greater attention in Europe and USA than in Japan. Finally, new molecular targeted agents are under investigation in patients with ATL.

Herein, we review current treatments for ATL, along with previous and future therapies.

Epidemiology

Approximately 10–20 million people are infected with HTLV-1 worldwide; endemic areas include Central Africa, South America, the Caribbean basin, Iran, south-western Japan and Melanesia.[11] In Japan, approximately 1.1 million individuals are infected with HTLV-1[12] and approximately 1000 HTLV-1 carriers develop ATL each year.[13]

In late 2000, a decrease in the prevalence of HTLV-1 carriers has been observed in the Kyushu district (south-western island of Japan, an endemic area for ATL); however, the prevalence is increasing in several regions in the non-endemic areas.[12] The age-standardized incidence rates of ATL in the Honshu region of Japan and the USA, both of which are considered non-endemic areas, are increasing significantly, although no changes in incidence have been observed in the Kyushu district.[14] These results suggest that HTLV-1 is spreading through the migration of carriers from endemic to non-endemic areas. The mortality (per 100 000 person-years)

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of patients with ATL decreased from 1.86 (95% confidence interval [CI]: 1.84–1.87) to 1.41 (95% CI: 1.40–1.43) in Kyushu during the period of 2000–2009, and from 0.22 (95% CI: 0.22–0.23) to 0.16 (95% CI: 0.16–0.17) in other areas of Japan from 2003–2009, and these trends are statistically significant.[13] The number of allo-HSCT performed in Japan has increased since 2000.[13] A significant inverse correlation was observed between the decreasing mortality trend and the increasing number of allo-HSCT procedures. The decreasing trend in mortality observed in ATL patients might be associated with allo-HSCT.[13]

Diagnosis and Clinical Subtype

A diagnosis of ATL is made by anti-HTLV-1 positivity in sera and by confirming the presence of a mature T-cell malignancy. The identification of monoclonal integration of HTLV-1 proviral DNA in tumor cells by Southern blot analysis is required to confirm a diagnosis of ATL.

Adult T-cell leukemia-lymphoma is divided into four clinical subtypes (acute, lymphoma, chronic and smoldering) according to leukemic manifestation in the blood, organ involvement, serum lactate dehydrogenase (LDH) levels and corrected serum calcium levels (Table 1).[5] Chronic type is divided into two subtypes: the unfavorable chronic type with at least one poor prognostic factor and the favorable chronic type with no poor prognostic factors. Poor prognostic factors include three factors, including serum LDH > upper limit of normal (ULN), serum blood urea nitrogen > ULN and serum albumin < lower limit of normal.[15]

Prognostic Factors and Stratification

The Lymphoma Study Group has identified five prognostic factors: age, total number of involved lesions, serum calcium level, serum LDH level and performance status (PS).[16] When ATL is stratified into three different groups (i.e. low risk group and high risk group based on the combination of prognostic factors, and extremely high risk group with high levels of serum calcium), OS is clearly different between the three groups. Nonetheless, these stratifications are not practical clinically as the classification system is rather complicated. In order to provide a more clinically useful system, Shimoyama devised a new clinical classification scheme for the four subtypes mentioned above.[5]

Several research groups in Japan have reported other factors that may also influence OS in ATL patients. These include deletion of *p16*, lung resistance-related protein and multi-drug resistance associated protein genes, eosinophilia, and expression of CC chemokine receptor 4 (CCR4) and serum interleukin (IL)-5.[17]

Recently, the Ann Arbor clinical stage, PS, and three continuous variables, age, serum albumin and soluble interleukin-2 receptor, were identified as independent prognostic factors in a multicenter retrospective analysis of 807 patients with newly diagnosed, acute-type and lymphoma-type ATL. Based on these results, Katsuya *et al.*[18] propose a prognostic index for acute-type and lymphoma-type ATL.

Treatment of Adult T-cell Leukemia-lymphoma

The current treatment strategy for patients with ATL is shown in Figure 1. Treatment is based on the clinical subtype. Patients with aggressive ATL, such as acute, lymphoma or chronic types, with at least one poor prognostic factor should receive early chemotherapy. In the USA and Europe, antiviral therapy using AZT/IFN is the standard treatment for leukemic-type ATL. In Europe, chemotherapy is the first-line therapy for lymphoma-type ATL, because OS with antiviral therapy alone is very short.[19]

Table 1. Diagnostic criteria for clinical subtype of adult T-cell leukemia-lymphoma

	Smoldering	Chronic§	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte ($\times 10^9$/L)	<4	≥4¶	<4	†
Abnormal T-lymphocytes	≥5%	+††	≤1%	+††
Flower cells of T-cell marker	Occasionally	Occasionally	No	+
LDH	≤1•5N	≤2N	†	†
Corrected Ca (mmol/L)	<2•74	<2•74	†	†
Histology-proven lymphadenopathy	No	†	+	†
Tumor lesion				
Skin	‡	†	†	†
Lung	‡	†	†	†
Lymph node	No	†	Yes	†
Liver	No	†	†	†
Spleen	No	†	†	†
CNS	No	No	†	†
Bone	No	No	†	†
Ascites	No	No	†	†
Pleural effusion	No	No	†	†
GI tract	No	No	†	†

†No essential qualification except terms required for other subtype(s). ‡No essential qualification if other terms are fulfilled, but histology-proven malignant lesion(s) is required in case abnormal T-lymphocytes are less than 5% in peripheral blood. §Chronic type is divided into two subtypes: the unfavorable chronic type with at least one poor prognostic factor and the favorable chronic type with no poor prognostic factors. Poor prognostic factors include three factors: serum LDH > upper limit of normal (ULN), serum BUN > ULN and serum albumin < lower limit of normal. ¶Accompanied by T-lymphocytosis ($3•5 \times 10^9$/L or more). ††In case abnormal T-lymphocytes are less than 5% in peripheral blood, histology-proven tumor lesion is required. Ca, calcium; CNS, central nervous system; GI, gastrointestinal; HTLV-1, human T-cell leukemia virus type-I; LDH, lactate dehydrogenase; N, normal upper limit. Source: Shimoyama (1991).

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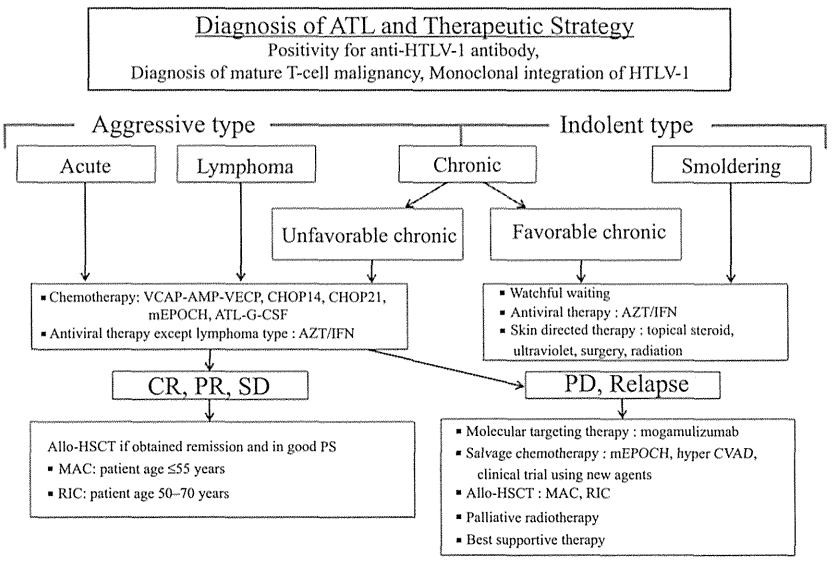

Fig. 1. Treatment algorithm for adult T-cell leukemia-lymphoma (ATL) patients. ATL diagnosis is based on anti-HTLV-1 antibody positivity in the serum, the presence of mature T-cell malignancy, and the Southern blot detection of monoclonal integration of HTLV-1 proviral DNA in the tumor cells. ATL treatment is usually determined according to the clinical subtypes and prognostic factors. The presence of an aggressive-type ATL (acute, lymphoma and chronic types with poor prognostic factors) or indolent-type ATL (chronic and smoldering types without poor prognostic factors) is critical when making treatment decisions. Patients with an aggressive-type (acute, lymphoma and unfavorable chronic type) generally receive immediate combination chemotherapy or antiviral therapy with zidovudine and interferon-α (AZT/IFN), except for those with the lymphoma type. The international consensus meeting primarily recommends the VCAP-AMP-VECP regimen. Other therapeutic regimens include CHOP14, CHOP21, mEPOCH and ATL-G-CSF. The patients undergo further treatment with allogeneic hematopoietic stem cell transplantation, which is particularly effective in young patients with good performance statuses, and those who have achieved remission before transplantation. In Japan, patients with an indolent-type ATL without any skin lesions are usually followed up under a watchful waiting policy until the disease transforms to an aggressive type. Antiviral therapy is frequently performed for favorable chronic and smoldering ATL patients in non-Japanese nations, and skin directed therapy is applied for smoldering ATL with skin manifestations. allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATL-G-CSF, combination chemotherapy consisting of vincristine, vindesine, doxorubicin, mitoxantrone, cyclophosphamide, etoposide, ranimustine, and prednisone with granulocyte-colony stimulating factor support; AZT/IFN, zidovudine and interferon-α; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP14 is performed every 2 weeks and CHOP21 is performed every 3 weeks); CR, complete remission; hyper CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MAC, myeloablative conditioning; mEPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) with modifications; PD, progressive disease; PR, partial remission; PS, performance status; RIC, reduced intensity conditioning; SD, stable disease; VCAP-AMP-VECP, vincristine, cyclophosphamide, doxorubicin and prednisone (VCAP)-doxorubicin, ranimustine and prednisone (AMP)-vindesine, etoposide, carboplatin and prednisone (VECP).

Chemotherapy

Several chemotherapy combinations have been investigated for ATL patients in Japan, although the median OS range was only 6–8.5 months.[20] The Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG) has conducted a number of clinical trials for ATL patients in Japan, with complete response (CR) rates of 17–43% and median OS of 5–13 months in prospective multicenter studies.[21] The JCOG-LSG conducted a randomized clinical trial in patients with aggressive ATL in which a VCAP-AMP-VECP regimen (Fig. 2) was compared to a biweekly doxorubicin, cyclophosphamide, vincristine and prednisone (CHOP14) regimen.[22] The VCAP-AMP-VECP regimen reduced one course of VCAP-AMP-VECP from the original LSG15 regimen and added cytarabine to the intrathecal administration of methotrexate and prednisone as a prophylaxis against central nervous system (CNS) relapse. The CR rate and median OS of the VCAP-AMP-VECP regimen and CHOP14 regimen were 40% (95% CI: 27.6–54.2) versus 25% (95% CI: 14.5–37.3), and 13 versus 11 months, respectively. The CR rate of the VCAP-AMP-VECP regimen was significantly higher than that of CHOP14. In terms of the OS, there was no significant difference in the two groups (hazard ratio [HR] = 0.751, 95% CI: 0.50–1.13).[22] The VCAP-AMP-VECP regimen is considered a standard chemotherapeutic regimen for aggressive ATL in Japan.

Stem Cell Transplantation

In general, autologous HSCT has not been successful because of ATL relapses or infectious complications.[23] We and other Japanese researchers have reported that allo-HSCT could improve the outcome of ATL,[7] mainly using conventional myeloablative regimens (MAC); however, high transplant-related mortality poses a challenge (Table 2).

Therefore, allo-HSCT with reduced intensity conditioning regimens (RIC) was prospectively evaluated. Okamura *et al.*[24] report the safety and feasibility of allo-HSCT with RIC using peripheral blood stem cells from an HLA-matched sibling donor in older patients with ATL who achieved remission after chemotherapy. A total of 29 patients were registered, and the 5-year OS rate was 34% (95% CI: 18–51), indicating the potential curability of the disease.[25] Unrelated bone marrow (uBM) and cord blood transplantation with RIC were also prospectively evaluated as alternative strategies to allo-HSCT; follow up is currently under way.

By 2012, more than 1000 ATL patients had received various types of allo-HSCT. Currently, approximately 120 ATL patients undergo allo-HSCT each year in Japan.[26] Based on the incidence rate,[27] approximately 10% of ATL patients receive allo-HSCT each year. Several related aspects have been reported in a nationwide retrospective study. Based on the stem cell sources, the 3-year OS rate was highest for patients with related HLA-matched donors (41%, 95% CI: 33–49), followed

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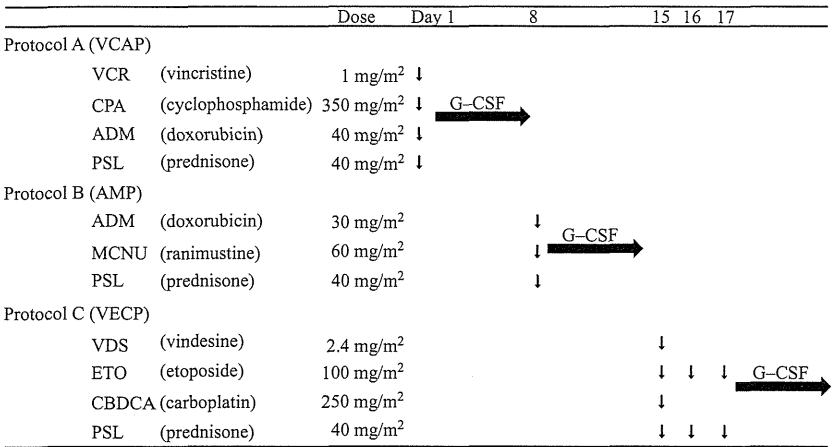

Fig. 2. The VCAP-AMP-VECP regimen. A, B and C are repeated every 28 days for 6 cycles. Cytarabine (40 mg), methotrexate (15 mg) and prednisone (10 mg) are administered intrathecally before cycles 2, 4 and 6. VCAP-AMP-VECP, vincristine, cyclophosphamide, doxorubicin and prednisone (VCAP)-doxorubicin, ranimustine and prednisone (AMP)-vindesine, etoposide, carboplatin and prednisone (VECP); G-CSF, granulocyte-colony stimulating factor.

by those with uBM (39%, 95% CI: 29–49).[28] In terms of the effect of acute graft-versus-host-disease (GVHD) on OS, grade I/II acute GVHD was significantly associated with a longer OS.[29] Regarding the effect of the conditioning regimen intensity on OS, although no significant difference was observed in the OS between MAC and RIC, a trend for superior OS was observed with RIC in older patients.[30] Bazarbachi *et al.*[31] report the results from the European Group for Blood and Marrow Transplantation's Lymphoma Working Party, and allo-HSCT might salvage ATL patients in non-Japanese patients.

Immunotherapy

Anti-tumor immune system activity has also been recognized in ATL patients who have received allo-HSCT.[29] Cytotoxic T-cells that targeted the HTLV-1 specific tax protein were detected in patients who were in remission after allo-HSCT.[32]

The discontinuation of immunosuppressive agents or donor lymphocyte infusions was effective in some ATL patients who relapsed after allo-HSCT; many of them developed GVHD subsequently.[33,34] The graft versus (Gv)-ATL effect, in particular the graft versus-tax (Gv-tax) effect after allo-HSCT, has been reported in ATL patients.[32] Therefore, immunotherapy targeting the tax protein may be effective in patients whose tumor cells express the tax protein. Indeed, a vaccine targeting tax was shown to induce anti-tumor activity in a mouse model.[35] Based on these findings, the anti-ATL vaccine, where the tax peptide is pulsed into autologous dendritic cells, was administered to three previously treated ATL patients as a clinical trial; the treated patients exhibited clinical effects without any serious adverse events except for a slight fever and transient skin reaction.[36] These results suggest that further improvements in immunotherapy are warranted.

Antiviral Therapy

Antiviral therapy using AZT/IFN was initially described by Gill *et al.*[8] and Hermine *et al.*[9] Gill *et al.* report an overall response rate (ORR) of 58% for 19 ATL patients, including 7 previously treated patients. Although a high ORR was achieved, the median OS of only 4.8 months in 12 of the previously untreated patients was considered unsatisfactory.[8] Subsequently, several follow-up studies of antiviral therapy using AZT/IFN have been conducted for ATL patients in Europe; however, the median OS could only be prolonged by 6–18 months.[37]

Bazarbachi *et al.* conducted a meta-analysis of antiviral therapy for ATL patients; they report that the median OS achieved with antiviral therapy was superior to that achieved with combination chemotherapy for ATL patients, especially for the leukemic subtypes, such as the smoldering, chronic and acute types of ATL.[19] Remarkably, a 5-year OS rate of 100% was achieved in patients with chronic and smoldering types of ATL with this antiviral therapy. It was concluded that antiviral therapy using AZT/IFN was the gold standard for the leukemic subtypes of ATL, although patients with the lymphoma type showed less benefit from antiviral therapy than from combination chemotherapy.[19,38] Takasaki *et al.*[39] report that the prognosis of indolent-type ATL in Japan is worse than that reported previously.[5] Bazarbachi *et al.*[19] report excellent results with antiviral therapy; therefore, it is important to verify the efficacy of antiviral therapy for Japanese ATL patients. Because the national health insurance system in Japan has not yet approved the use of these two drugs in the treatment of ATL patients, a randomized phase III clinical trial was recently initiated by the JCOG-LSG for treating indolent-type ATL with antiviral therapy consisting of AZT and IFN versus watchful waiting. This clinical trial will provide conclusive information regarding the optimal standard treatment for indolent-type ATL.

Molecular Targeted Therapy

Anti-CCR4 antibody therapy. The overexpression of CCR4 has been reported in tumor cells of various lymphoid neoplasms. The ratio of expression varies among different disease entities and is higher in mature T-cell and NK-cell neoplasms. Approximately 90% of ATL cases are CCR4-positive.[40] CCR4 expression has also been shown to affect the prognosis of ATL patients; multivariate analysis revealed that CCR4 positivity was a significant unfavorable prognostic factor.[40]

Mogamulizumab (KW-0761) is a first-in-class defucosylated humanized anti-CCR4 monoclonal antibody that has been generated by protein engineering;[41] mogamulizumab shows highly potent ADCC activity because of its high affinity of binding to effector cells, including NK cells.

Based on the phase I study, a phase II study for CCR4-positive relapsed ATL was conducted in Japan wherein 1.0 mg/kg of mogamulizumab was intravenously administered once a

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Table 2. Summary of published reports on allogeneic hematopoietic stem cell transplantation in ATL

Reference	Patient Number	Median age (range)	Sex M/F	Subtype	Donor	Donor HTLV-1 Ab	Stem cell source	Disease Status at SCT	Conditioning regimen	Cause of death	Outcome
Utsunomiya (BMT, 2001)	10	45 (33–51)	7/3	Acute: 8 Lymphoma: 1 Other: 1	MSD: 9 MUD: 1	Neg: 7 Posi: 3	BM: 8 PB: 1 BM + PB: 1	CR: 4 PR: 5 NR: 1	MAC: 10	TRM: 4	Median leukemia-free survival 17.5+ M (range 3.7–34.4+)
Kami (BJH, 2003)	11	47 (15–59)	7/4	Acute: 5 Lymphoma: 4 Other: 2	MSD: 9 PMRD: 1 MUD: 1	Neg: 9 Posi: 2	BM: 7 PB: 3 BM + PB: 1	CR: 6 PR: 1 PD: 4	MAC: 9 RIC: 2	TRM: 7	1Y-OS 54.5 ± 30.0%
Fukushima (Leukemia, 2005)	40	44 (28–53)	22/18	Acute: 30 Lymphoma: 10	MSD: 27 PMRD: 5 NUD: 8	Neg: 27 Posi: 9 NE: 4	BM: 21 PB + 19	CR: 15 PR: 13 NC: 3 PD: 9	MAC: most cases	TRM: 16 Unk: 1 ATL: 4	3Y-0S 45.3%
Kato (BBMT, 2007)	33	49 (24–59)	18/15	Acute: 20 Lymphoma: 7 NE: 6	MUD: 33	Neg: 33	BM: 33	CR + PR: 15 NR: 14 NE: 4	MAC: 27 RIC: 6	TRM: 9 ATL: 2 NE: 3	1Y-OS 49.5%
Shiratori (BBMT, 2008)	15	57 (41–66)	3/12	Acute: 6 Lymphoma: 8 Other: 1	MSD: 10 MRD: 5	Neg: 13 Posi: 2	BM: 8 PB: 4 BM + PB: 3	CR: 9 PR: 5 PD: 1	MAC: 5 RIC: 10	TRM: 2 ATL: 2	3Y-OS 73.3%
Nakase (BMT, 2006)	8	49 (45–59)	2/6	Acute: 5 Lymphoma: 3	MUD: 3 PMUD: 5	Neg: 8	BM: 8	CR: 6 Non-CR: 2	MAC: 5 RIC: 3	TRM: 2 ATL: 1	Median OS 20M (range 0-43)
Nakamura (IJH, 2012)	10	51 (31–64)	6/4	Acute: 9 Lymphoma: 1	PMUD: 10	Neg: 10	UCB	CR: 2 PR: 4 SD: 1 PD: 3	MAC: 6 RIC: 4	ATL: 4 Sepsis: 1 GVHD+ATL: 1	2Y-OS: 40% (95% CI 67-12)
Fukushima (IJH, 2013)	27	52 (41–63)	18/9	Acute: 17 Lymphoma: 10	MUD: 1 PMUD: 26	Neg: 27	UCB	CR: 5 PR: 11 RIF: 5 REL: 6	MAC: 9 RIC: 18	TRM: 10 ATL: 9	3Y-OS: 27.4%
Bazarbachi (BMT, 2014)	17	47 (21–58)	9/8	Acute: 5 Lymphoma: 10 Chro/Smold: 2	MSD: 6 MUD: 7 UnK: 1 PMRD: 3	ND	ND	CR: 9 PR: 4 PD: 4	MAC: 4 RIC: 13	ATL: 8 GVHD: 2 Sepsis: 1	3Y-OS: 34.3%

ATL, adult T-cell leukemia-lymphoma. BBMT, *Biology of Blood and Marrow Transplantation*; BJH, *British Journal of Haematology*; BMT, bone marrow transplantation; Chro/Smold, chronic /smoldering; CR, complete remission; GVHD, graft-versus-host disease; IJH, *International Journal of Hematology*; M, month; MAC, myeloablative conditioning; MSD, HLA-matched sibling donor; MUD, HLA-matched unrelated donor; NC, no change; ND, not described; NE, not evaluable; Neg, negative; NR, no response; OS, overall survival; PD, progressive disease; Posi, positive; PMRD, HLA partially matched related donor; PMUD, HLA partially matched unrelated donor; PR, partial remission; RIC, reduced intensity conditioning; SCT, stem cell transplantation; SD, stable disease; TRM, transplant-related mortality; UCB, unrelated cord blood; UnK, unknown.

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week for 8 weeks; of the 26 patients evaluable for efficacy assessment, the ORR was 50% (95% CI: 30–70), and response rates according to disease lesions were 100% for blood, 63% for skin, and 25% for nodal and extranodal lesions. The median progression-free survival and OS were 5.2 and 13.7 months, respectively.[42] Subsequently, a randomized clinical trial was conducted for evaluating VCAP-AMP-VECP treatment with or without mogamulizumab in newly diagnosed CCR4-positive aggressive ATL patients in Japan. Combination therapy with VCAP-AMP-VECP plus mogamulizumab demonstrated a CR rate of 52% (95% CI: 33–71), which was 19% higher than treatment with VCAP-AMP-VECP alone (33%, 95% CI: 16–55).[43]

Although mogamulizumab was very effective for relapsed ATL, adverse drug reactions, including infusion reaction (89%) and skin rash (63%), were frequently observed in the phase II study. Severe skin rash was observed occasionally, and one patient developed Stevens-Johnson syndrome during the phase II study.[42]

Molecular targeted therapy with small molecules. Recently, molecular targeted therapy with small molecules, such as tyrosine kinase inhibitors, angiogenesis inhibitors and proteasome inhibitors, has been applied for various malignancies. The proteasome inhibitor bortezomib has been reported to suppress the growth of ATL cell lines and freshly isolated ATL cells;[44] a trial for relapsed or refractory ATL patients is currently under way in Japan to investigate the clinical efficacy of bortezomib.

Supportive Therapy

Hypercalcemia associated with disease progression and opportunistic infections caused by immunodeficiency are problematic events in ATL patients.[5] Patients with hypercalcemia need immediate treatment with hydration, antidiuretics, calcitonin, steroid hormones and bisphosphonates. Furthermore, urgent chemotherapy using anti-cancer agents for ATL is needed in severe cases of hypercalcemia.

As CNS relapse is known to occur frequently in ATL patients, the intrathecal administration of the anti-cancer agents methotrexate, cytarabine and prednisone is required for prophylaxis.[22]

Opportunistic infections from bacteria, fungi, virus, protozoans and parasites are frequently observed in ATL patients, and appropriate treatment is needed.[5] In Japan, prophylactic treatment includes the use of fluconazole for *Candida*, itraconazole for *Aspergillus* and trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*.

Recent Findings of Genomic Heterogeneity of Adult T-cell Leukemia-lymphoma Cells

The initial pathogenic event for ATL is HTLV-1 integration; however, additional genetic alterations in ATL have also been implicated in its pathogenesis.[45] Umino *et al.*[46] recently reported the clonal heterogeneity of ATL tumor cells involving different genomic alterations; they demonstrated that these cells originated from a common cell. It was suggested that approximately 70% of ATL cases undergo clonal evolution, and that genetic instability may attribute to the accumulation of genomic alterations. The existence of multiple clones with genomic instability is one factor that renders ATL cells resistant to conventional chemotherapy. Even if a proportion of cells are killed by chemotherapy, there is always the possibility that a new resistant clone will emerge. Therefore, it is feasible to use allo-HSCT that can cure ATL patients by eliminating the HTLV-1-integrated recipient ATL clones through immune reaction, and by replacing the hematopoietic system with the donor type. Whole genome sequencing revealed that carriers have 10^3 to 10^4 orders of distinct clones with different HTLV-1 integration sites, and that most clones harbored one copy of HTLV-1.[47] This indicates that HTLV-1 carriers potentially have 10^3 to 10^4 malignant clones. If the number of pre-malignant cells increases, there is a greater possibility that malignant transformation can occur. Therefore, it is important to reduce the number of pre-malignant cells in carriers of HTLV-1 in order to prevent the development of ATL.

Prevention of Adult T-cell Leukemia-lymphoma Development

An ongoing nationwide prospective investigation (Joint Study on Predisposing Factors of ATL Development) was initiated in 2001 to identify HTLV-1 carriers with the highest risk of developing ATL. Four risk factors have been associated with ATL development in HTLV-1 carriers, including age ≥40 years, high HTLV-1 proviral loads in peripheral blood mononuclear cells, family history of ATL, and any clinical signs or symptoms.[48] Although it is obviously very important to prevent the development of ATL in HTLV-1 carriers with any of these risk factors, there are currently no available means towards this end.

The prevention of HTLV-1 infection is also of utmost importance because ATL is caused by HTLV-1 infection. HTLV-1 infection is thought to be transmitted by breastfeeding from the mother to infant, sexual intercourse or blood transfusion. The incidence of ATL development in HTLV-1 carriers differs according to the route of infection.[49] A nationwide prospective study is currently under way in Japan using three different nursing methods: cessation of breastfeeding, short nursing periods and ordinary nursing.

Future Directions

Histone deacetylase (HDAC) inhibitors, such as vorinostat (suberoylanilide hygroxamic acid: SAHA), panobinostat (LBH-589) and MS-275, have been recognized for their abilities to inhibit HTLV-1-infected cell lines and freshly isolated ATL cells.[50] Clinical use of these HDAC inhibitors for the treatment of ATL patients is expected.

Furthermore, various combinations of treatment, including chemotherapy, allo-HSCT, immunotherapy and molecular targeted therapies may help to cure a higher proportion of ATL patients in the future.

Conclusions

Although new therapeutic options are gradually improving the curability of ATL, treatment remains challenging for ATL patients. Nevertheless, to increase the ATL cure rate, rigorous investigation is necessary for optimizing therapeutic combinations, prevention of ATL development in HTLV-1 carriers, and reduction in the number of HTLV-1 carriers.

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Disclosure Statement

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LETTER TO THE EDITOR

High incidence of CMV infection in adult T-cell leukemia/lymphoma patients after allogeneic hematopoietic stem cell transplantation

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CMV diseases are one of the significant factors contributing to morbidity and mortality in recipients of allogeneic hematopoietic stem cell transplantation (HSCT).[1] Preemptive therapy for active CMV infection based on monitoring CMV pp65 antigenemia and/or CMV-DNA PCR assay has been attempted.[2] In Japan, only the CMV pp65 antigenemia test is covered by the National Health Insurance program. Adult T-cell leukemia/lymphoma (ATLL), which is a human T-lymphotropic virus type I-related hematological malignancy, is known to have a poor prognosis. So far there have only been a few reports about the incidence of CMV infection in ATLL patients following allogeneic HSCT.[3] Here we have analyzed the incidence of CMV infection and related clinical issues in 52 allogeneic HSCT recipients.

Eighty-five patients, who survived at least 30 days after HSCT, consecutively underwent allogeneic HSCT from November 2006 to May 2012 at Imamura Bun-in Hospital, Kagoshima, Japan. Thirty-three patients were excluded from this study for lack of necessary data. The remaining 52 (male: 34, female: 18) patients were analyzed as below (Table 1).

The diagnosis of CMV infection was confirmed with the CMV pp65 antigenemia test, in which one or more CMV-positive cells were detected in a peripheral blood sample of 50 000 white blood cells. Statistical analysis was carried out using the 'EZR' (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).[4] Comparison between ATLL patients and non-ATLL patients was carried out for each variable (Table 1). Gender, age, disease status, conditioning regimen, steroid usage and incidence of CMV disease were estimated according to the Mann–Whitney *U*-test, while stem cell source, GVHD prophylaxis and CMV-IgG serostatus were estimated using Fisher's exact test. A disease status of high risk was defined as not in CR (non-CR) for all hematological malignant diseases and in high risk of myelodysplastic syndrome as defined by the International Prognostic Scoring System. All other disease statuses were defined as standard risk. For the risk evaluation of CMV infection, patient group with CMV-IgG serostatus of donor − /recipient − was considered as low risk, and all others were defined as high risk status. The probability of CMV infection was estimated based on cumulative incidence curves. The competing event was death without CMV infection. The groups were compared using Gray's test. The Fine–Gray proportional hazards model was used to determine the significance of multivariables in determining the incidence of CMV infection. Statistical significance was defined as $P < 0.05$.

Twenty-three ATLL patients and 29 non-ATLL patients (of which 12 had AML, 10 myelodysplastic syndrome, 3 non-Hodgkin lymphoma, 2 had ALL, 1 aplastic anemia and 1 multiple myeloma) were included in our study. No patient received ganciclovir or Foscavir as prophylaxis. Median age at allogeneic HSCT was 54 years (range 19–69). Thirteen patients were transplanted from sibling donors (of which 6 were BM and 7 peripheral blood) and 39 patients from unrelated donors (of which 31 were BM and 8 umbilical cord blood). Thirty-eight patients had received a myeloablative conditioning regimen and 14 a reduced intensity conditioning regimen (RIC) before allogeneic HSCT (Table 1). All of the recipients of sibling donor transplants received CsA and short-term MTX as the GVHD prophylaxis. Tacrolimus and short-term MTX were administered in all of the unrelated BM recipients. With respect to GVHD, 15 patients suffered any grade of GVHD. Twelve of 15 patients were grade II–IV and 5 were grade III–IV. In addition, tacrolimus and mycophenolate mofetil were administered to all of the umbilical cord blood recipients except one who received tacrolimus alone. The details of CMV-IgG serostatus are described in Table 1. Thirty of 52 patients received steroids within 10 days before the incidence of CMV infection, including 16 patients who received over 1 mg/kg steroid for GVHD treatment and the remaining 14 patients received low-dose steroid for not only GVHD treatment, but also prophylaxis for fever and drug allergies (Table 1). Five patients developed CMV diseases (4 colitis and 1 pneumonia) and no significant difference was observed between ATLL and non-ATLL patients (Table 1).

Thirty-nine patients (20 ATLL and 19 non-ATLL) were diagnosed with CMV infection. The probability of CMV infection was 87% in ATLL patients compared with 68.9% in non-ATLL patients ($P = 0.004$), 87.9% in age $\geqslant 50$ years vs 52.6% in < 50 years ($P = 0.021$), 93.8% in steroid-users of a dose of over 1 mg/day vs 68.2% in others ($P = 0.001$), 93.3% in steroid-users in any dose of steroid vs 52.2% in non-users ($P < 0.001$) and 100% in RIC vs 66.5% in myeloablative conditioning regimen ($P = 0.001$). In the multivariate analysis, ATLL (HR: 3.696, 95% CI: 1.535–8.898; $P = 0.004$), steroid usage (HR: 3.683, 95% CI: 1.297–10.46; $P = 0.014$) and RIC (HR: 2.394, 95% CI: 1.100–5.212; $P = 0.028$) were the significant factors for occurrence of CMV infection (Table 2).

The incidence of CMV infection was high in allogeneic HSCT recipients with ATLL compared with non-ATLL patients in our study. Ogata *et al.*[5] previously reported that CMV reactivation was common in ATLL patients receiving chemotherapy. With respect to the relationship between age and serostatus, although only 6 of 12 non-ATLL recipients whose ages were < 50 years, were seropositive, all of the same group of ATLL recipients were seropositive before transplantation. These results indicated that ATLL patients typically have a CMV-compromised immune system.

In our study, there was no difference in incidence of CMV diseases between ATLL patients and non-ATLL patients. This result might indicate that preemptive therapy based on monitoring CMV pp65 antigenemia test successfully prevented HSCT recipients from contracting CMV diseases in both the groups.

RIC regimens were a significant factor for incidence of CMV infection, which was a different result from previous reports.[6,7] There is a possibility that the remaining infected lymphocytes after RIC are responsible for CMV infection after transplantation.

Previous reports showed that steroid administration is a risk factor for CMV infection.[8] Despite no significant difference being observed between steroid usage in ATLL patients and non-ATLL patients, usage of steroid was a significant factor in our study. Therefore, although the limitation of this study is the small number of patients, ATLL could be one of the disease-specific risk factors for CMV infection.

Table 1. Patients' characteristics

Variables	*Total (n = 52)*	*ATLL (n = 23)*	*Non-ATLL (n = 29)*	*P-value*
Gender				0.554
Male	34	14	20	
Female	18	9	9	
Age				0.956
Median (range), years	54 (19–69)	54 (34–65)	54 (19–69)	
Disease status				0.021
High risk	29	17	12	
Standard risk	23	6	17	
Stem cell sources				0.078
Sib-BM	6	5	1	
Sib-PB	7	3	4	
UBM	31	14	17	
UCB	8	1	7	
Conditioning regimen				0.736
MAC	38	16	22	
RIC	14	7	7	
GVHD prophylaxis				0.147
TAC+sMTX	31	14	17	
CsA+sMTX	13	8	5	
TAC+MMF	7	1	6	
TAC alone	1	0	1	
Incidence of acute GVHD				
Grade II–IV	12	6	6	0.659
Grade III–IV	5	4	1	0.097
Steroid usage within 10 days before CMV infection				
Any dose	30	14	16	0.338
More than 1 mg/kg	16	8	8	0.588
CMV-IgG serostatus				0.157
Donor−/recipient−	4	0	4	
Donor−/recipient+	20	9	11	
Donor+/recipient−	5	1	4	
Donor+/recipient+	23	13	10	
CMV disease	*5*	*2*	*3*	0.483
Colitis	4	1	3	
Pneumonia	1	1	0	

Abbreviations: ATLL = adult T-cell leukemia/lymphoma; MAC = myeloablative conditioning regimen; MMF = mycophenolate mofetil; RIC = reduced intensity conditioning regimen; sMTX = short-term MTX; Sib = sibling; TAC = tacrolimus; UCB = umbilical cord blood; UBM = unrelated BM. Comparison among groups was carried out in each item. ATLL patients showed dominantly high-risk disease status compared with non-ATLL patients.

Table 2. Multivariate analysis on the incidence of CMV infection

Variables	*Multivariate analysis*		
	HR	*95% CI*	*P-value*
Age			
⩾50	1.060	0.299–3.757	0.930
Gender			
Female	1.059	0.583–2.123	0.870
Disease status			
High risk	0.837	0.342–2.050	0.700
Disease			
ATLL	**3.781**	**1.514–9.444**	**0.004**
CMV-IgG serostatus			
Low risk	0.474	0.171–1.321	0.150
Stem cell source			
Non-CB	0.870	0.263–2.874	0.820
Conditioning regimen			
RIC	**2.433**	**1.099–5.390**	**0.028**
Incidence of GVHD			
Grade II–IV	1.498	0.360–6.236	0.580
Grade III–IV	0.783	0.241–2.540	0.680
Steroid usage			
Any dose	**4.006**	**1.182–13.58**	**0.026**
More than 1 mg/kg	0.988	0.223–4.373	0.990

Abbreviations: ATLL = adult T-cell leukemia/lymphoma; CI = confidence interval; CB = cord blood; RIC = reduced intensity conditioning regimen. Multivariate analysis for the incidence of CMV infection was carried out with the Fine–Gray proportional hazard model. ATLL and steroid usage were the significant factors for the incidence of CMV infection. The results with statistical significance were highlighted in bold.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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High Level of Serum Soluble Interleukin-2 Receptor at Transplantation Predicts Poor Outcome of Allogeneic Stem Cell Transplantation for Adult T Cell Leukemia

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A B S T R A C T

The prognosis for adult T cell leukemia/lymphoma (ATL) is very poor, and only allogeneic hematopoietic stem cell transplantation (allo-SCT) has been considered to be a curative treatment for ATL. In this study, we retrospectively analyzed data for patients who had received allo-SCT for ATL in Hokkaido, the northernmost island of Japan, to determine prognostic factors. Fifty-six patients with a median age of 57 years received allo-SCT. Twenty-eight (50.0%) patients had acute type and 22 (46.4%) had lymphoma type. Twenty-three (41.1%) patients received allo-SCT in complete remission (CR), whereas the others were in non-CR. Seventeen (30.4%) patients received myeloablative conditioning and the others received reduced-intensity conditioning. With a median follow-up period of 48 months (range, 17 to 134 months), 1-year overall survival (OS) and 5-year OS rates were 55.4% and 46.1%, respectively. The survival curve reached a plateau at 22 months after stem cell transplantation (SCT). Male sex, high level of serum soluble interleukin-2 receptor (sIL-2R) at SCT, and non-CR at SCT were determined to be significant risk factors for OS. A high level of sIL-2R at SCT was a risk factor for poor OS in patients with non-CR at SCT by univariate analysis ($P = .02$), and it remained significant after adjustment by sex (hazard ratio, 2.73 [95% confidence interval, 1.07 to 7.90]). A high level of sIL-2R at SCT was also determined to be a risk factor for disease progression ($P = .02$). This region-wide study showed encouraging results for survival after allo-SCT for ATL and demonstrated for the first time that a high level of sIL-2R at SCT predicts worse SCT outcome.

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INTRODUCTION

Adult T cell leukemia/lymphoma (ATL) is a peripheral T cell lymphoma caused by human T cell lymphotropic virus type 1 (HTLV-1), and the prognoses of aggressive subtypes (acute type and lymphoma type) of ATL are very poor [1]. Although only allogeneic hematopoietic stem cell transplantation (allo-SCT) has been considered to be a curative treatment for aggressive subtypes of ATL [2], less than 40% of patients who have received allo-SCT have been cured [3-5]. We previously reported excellent outcomes for ATL patients who received allo-SCT from 2 institutions in Hokkaido, the northernmost island of Japan [6], and overall survival (OS) rate in that study was 73.3% at 3 years after allo-SCT. We, therefore, conducted a region-wide retrospective study in this area to determine prognostic factors for patients with ATL who received allo-SCT.

PATIENTS AND METHODS

Collection of Data

Clinical data for 56 patients who received allo-SCT for ATL between January 2000 and March 2012 were collected from all stem cell transplantation (SCT) centers in Hokkaido, Japan. The patients included all patients with ATL who received allo-SCT in this area. This study was conducted with the approval of the institutional review board of Hokkaido University Hospital. Conditioning regimens and other procedures of SCT were performed according to the decision of the clinicians at each center.

Definitions

Shimoyama's classification was used for the definition of ATL subtypes [7]. Neutrophil engraftment and platelet engraftment were defined as the first of 3 days with absolute neutrophil count $> .5 \times 10^9$/L and the first of 7 days with an untransfused platelet count $> 50 \times 10^9$/L, respectively. The hematopoietic cell transplant comorbidity index was scored by the criteria previously described [8]. Acute graft-versus-host disease (AGVHD) and chronic GVHD (CGVHD) were graded by standard criteria [9,10]. Transplantation-related mortality (TRM) was defined as any death other than death from ATL. OS was calculated from the day of SCT until death or last follow-up. Progression of ATL was defined as relapse after remission, development of new lesions, or increase in measurable disease or in the number of

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circulating leukemic cells by 25% or more [11]. Progression-free survival (PFS) was defined as survival without progression of ATL.

Endpoint and Statistical Analysis

The primary endpoint of this study was OS rate of the patients. Descriptive statistical analysis was performed using the chi-square test or Fisher's exact test as appropriate for categorical variables and using the 2-sided Wilcoxon rank-sum test for continuous variables. The probabilities of OS and PFS were estimated using the Kaplan-Meier method. Disease progression rates and TRM rates were estimated using cumulative incidence analysis and considered as competing risks, and Gray's test was used for group comparison of cumulative incidence. The effects of various patient and disease categorical variables on survival probabilities were examined using the log-rank test, and the following variables were included in subgroup analyses: age of the patients, sex of the patients, levels of serum soluble interleukin-2 receptor (sIL-2R) at diagnosis and SCT, disease status at SCT, disease subtypes, months from diagnosis to SCT, levels of lactate dehydrogenase (LDH) at diagnosis and at SCT, donor, stem cell source, intensity of the conditioning regimen, GVHD prophylaxis, and CGVHD. All P values were 2-sided and a P value of .05 was used as the cutoff for statistical significance. Multivariate analysis for OS was performed using the Cox proportional hazards regression model.

RESULTS

Patients and Transplantation Characteristics

Patients and SCT characteristics are summarized in Table 1. The median age of the patients was 57 years, and one half of the patients were male. Twenty-eight (50.0%) patients had acute type and 22 (46.4%) patients had lymphoma type. HTLV-1 serostatus of donors were available in 47 patients, and only 2 (4.3%) donors were positive for HTLV-1. After induction chemotherapies that were mainly CHOP or VCAP-AMP-VECP regimens [12], 23 (41.1%) patients received allo-SCT in complete remission (CR) and 33 (58.9%) patients received allo-SCT in non-CR. Nineteen patients had high level of sIL-2R at SCT. Among the patients with high level of sIL-2R at SCT, only 1 patient was in CR at SCT and the other 18 patients were not in CR at SCT. There was a correlation between disease status at SCT and sIL-2R at SCT (median, 824 U/mL [range, 351 to 2530] in CR patients versus a median of 2325 U/mL [range, 435 to 37,384 U/mL] in non-CR patients; P = .02). Seventeen (30.4%) patients received myeloablative conditioning, which consisted of high-dose cyclophosphamide and total body irradiation with or without VP-16, and 39 (69.6%) patients received reduced-intensity conditioning, which consisted of fludarabine with either busulfan or melphalan ±low-dose total body irradiation of 2 to 4 Gray.

Table 1
Patient and Transplantation Characteristics

Characteristics (n = 56)	Value
Age, median (range), yr	57 (37-69)
Age ≥ 60	37 (66.1%)
Sex	
Male	28 (50.0%)
Female	28 (50.0%)
Disease subtype	
Acute	28 (50.0%)
Lymphoma	26 (46.4%)
Chronic	1 (1.8%)
Smoldering	1 (1.8%)
WBC count at diagnosis, median (range), per μL	10,900 (2500-331,000)
LDH level at diagnosis, median (range), IU/L	352 (144-1736)
sIL-2R level at diagnosis, median (range), per mL	11,153 (998-116,100)
Months from diagnosis to SCT, median (range)	196 (60-3690)
≤ 3 months	7 (12.5%)
3-6 months	17 (30.4%)
> 6 months	32 (57.1%)
Disease status at SCT	
CR	23 (41.1%)
Non-CR	33 (58.9%)
PR	19 (33.9%)
REF	10 (17.9%)
REL	4 (7.1%)
LDH level at diagnosis, median (range), IU/L	218 (150-766)
sIL-2R level at SCT, median (range), U/mL	1219 (351-37,387)
HCT-CI score*	
0	22 (41.5%)
1	11 (20.8%)
2	9 (17.0%)
3	6 (11.3%)
4-7	5 (9.4%)
Donor	
MRD	20 (35.7%)
MUD	22 (39.3%)
MMD	14 (25.0%)
Sex disparity	
Match	32 (57.1%)
Mismatch	24 (42.9%)
Male to female	15 (26.8%)
Female to male	9 (16.1%)
Stem cell source	
BM	39 (69.6%)
PBSC†	11 (19.6%)
CB	6 (10.7%)
Conditioning regimen	
MAC	17 (30.4%)
RIC	39 (69.6%)
TBI	
Yes	40 (71.4%)
No	16 (28.6%)
GVHD prophylaxis	
CSP+MTX	22 (39.3%)
TK+MTX	25 (44.6%)
CSP alone or TK alone	7 (12.5%)

WBC indicates white blood cell; LDH, lactate dehydrogenase; SCT, stem cell transplantation; sIL-2R, soluble interleukin-2 receptor; CR, complete remission; PR, partial remission; REF, primary refractory; REL, relapse; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; MMD, HLA-mismatched donor; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; LDH lactate dehydrogenase; HCT-CI, hematopoietic cell transplant comorbidity index; TBI, Total body irradiation; GVHD, graft-versus-host disease; CSP, cyclosporin A; MTX, methotrexate; TK, tacrolimus. Data presented are n (%) unless otherwise indicated.

* HCT-CI score was not available in 3 patients.

† PBSC were from an MRD in all cases because donation of PBSC from unrelated donors is not permitted in Japan until 2010.

Transplantation Outcomes

Engraftment and GVHD

Except for 3 patients who died before engraftment, 53 (94.6%) patients achieved neutrophil engraftment at a median of 16 (range, 9 to 31) days. Platelet engraftment could be assessed in 52 patients, and 40 (76.9%) patients achieved platelet engraftment at a median of 27 (range, 14 to 415) days. All patients who achieved neutrophil engraftment were assessed for AGVHD. Overall AGVHD, grade II to IV AGVHD, and grade III to IV AGVHD occurred in 40 (75.5%), 31 (58.5%), and 8 (15.1%) of the evaluable patients, respectively. The median onset of AGVHD was 29 (range, 8 to 101) days. CGVHD was assessed in 43 patients who survived beyond day 100 after SCT. CGVHD occurred in 24 (55.8%) of the evaluable patients at a median onset day of 168 (range, 69 to 495) days, and extensive CGVHD occurred in 16 patients (37.2%).

Disease progression and TRM

Cumulative incidences of disease progression and TRM are shown in Figure 1. Fourteen (25.0%) patients showed disease progression at a median of 74 (range, 12 to 273) days after SCT. Twelve patients with disease progression after SCT died of ATL. One of the other 2 patients with disease progression died of a transplantation-related complication in

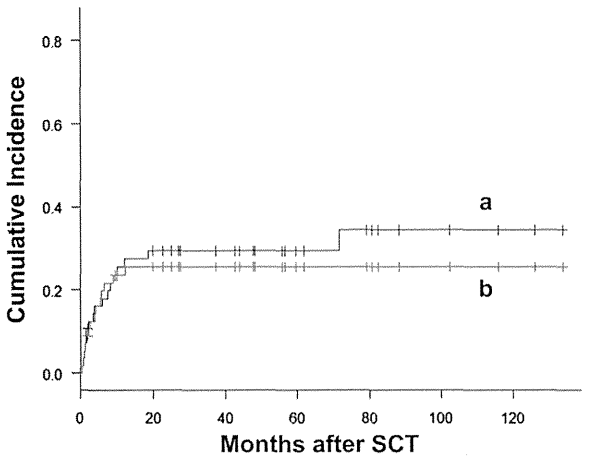

Figure 1. Cumulative incidence analyses of disease progression and TRM after SCT. Cumulative incidences of (a) TRM and (b) disease progression after allo-SCT. Disease progression and TRM were considered as competing risks.

remission and the other is alive in remission. The median time from disease progression to death was 92 (range, 32 to 399) days. Eighteen (32.1%) patients died of TRM at a median of 148 (range, 12 to 2143) days. The causes of TRM included infection (n = 6), AGVHD (n = 4), veno-occlusive disease (n = 2), CGVHD (n = 2), thrombotic microangiopathy (n = 1), cerebral infarction (n = 1), chronic renal failure (n = 1), and suicide (n = 1). Univariate analysis showed that a high level of sIL-2R at SCT (≥ 2000 U/mL) was significantly associated with disease progression ($P = .02$), whereas male sex tended to be associated with increased risk ($P = .06$). Non-CR at SCT was marginally significant for TRM ($P = .07$).

Survival

The median follow-up period for survivors was 48 (range, 17 to 134) months. One-year OS and 5-year OS rates were 55.4% and 46.1%, respectively. One-year PFS and 5-year PFS were 51.1% and 45.6%, respectively. The survival curve reached a plateau at 22 months after SCT (Figure 2). Male sex ($P = .002$), a high level of sIL-2R both at diagnosis (≥ 10,000 U/mL,

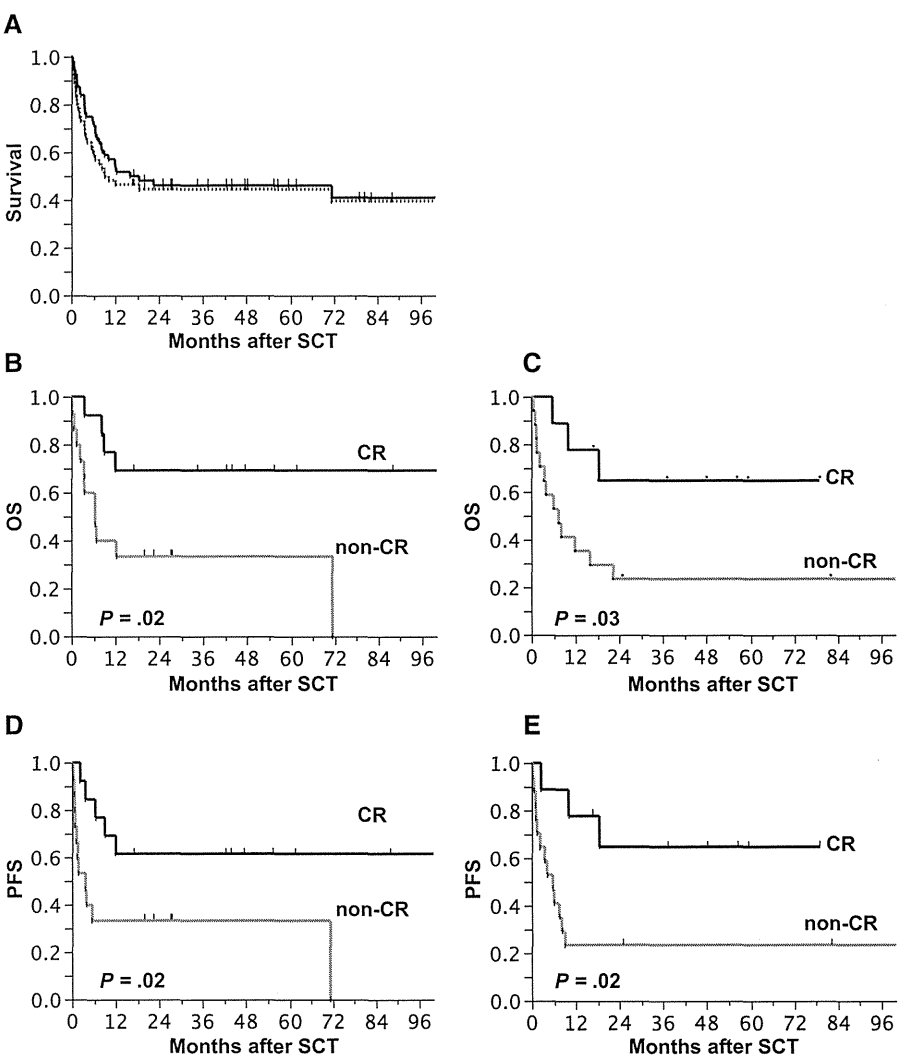

Figure 2. Survival after SCT. (A) Overall survival and progression-free survival after SCT in all patients. The solid line shows the overall survival curve and the dotted line shows the progression-free survival curve. (B) Overall survival in patients with acute type according to disease status at SCT. (C) Overall survival in patients with lymphoma type according to disease status at SCT. (D) Progression-free survival in patients with acute type according to disease status at SCT. (E) Progression-free survival in patients with lymphoma type according to disease status at SCT.

$P=.02$) and at SCT (≥ 2000 U/mL, $P<.001$) (Figure 3), and non-CR at SCT ($P<.001$) were identified as significant risk factors for OS by univariate analyses. Disease subtypes and other factors were not risk factors for OS. We tested several cutoff points of sIL-2R for determining the most significant cutoff points for survival and found that the cutoff levels of 10,000 at diagnosis and 2000 at SCT were most significantly associated with survival. Worse survival for male patients and patients in non-CR at SCT were confirmed by using multivariate analysis (hazard ratio, 3.40 [95% confidence interval (CI), 1.44 to 8.02] for male patients; hazard ratio, 4.45 [95% CI, 1.82 to 10.87] for non-CR patients). The levels of sIL-2R at SCT were not included in multivariate analysis, which included disease status, because the levels of sIL-2R at SCT were correlated with the disease status at SCT. In patients in non-CR at SCT, the level of sIL-2R was significantly associated with OS ($P = .02$) (Figure 3B), regardless of disease subtype ($P = .02$ for acute type and $P=.01$ for lymphoma type) (Figure 3C,D), and a high level of sIL-2R at SCT was determined to be a prognostic factor when it was used as an alternative variable to disease status at SCT in multivariate analysis (hazard ratio, 5.95 [95% CI, 2.14 to 17.9]). We performed multivariate analysis for non-CR patients using a level of sIL-2R at SCT and sex of the patients as variables, and a high level of sIL-2R at SCT remained significant even after adjustment by sex of the patients (hazard ratio, 2.73 [95% CI, 1.07 to 7.90]). The other variables were not confirmed to be significant by multivariate analysis.

DISCUSSION

A previous retrospective study on allo-SCT for ATL in Japan [4] demonstrated 3-year OS of 36.0%, and a prospective study on allo-SCT using a reduced-intensity conditioning regimen showed 5-year OS of 34.0% [5]. The 5-year OS rate in the present study was 46.1% and the survival curve reached a plateau at 22 months after SCT. Although the results of the present study are worse than the results we previously reported [6], the difference in results is probably due to the selection bias of the patients or might simply reflect a multi-institutional study versus a selected institutional study.

In previous nationwide studies on ATL in Japan, advanced age, male sex, non-CR at SCT, poor performance status, SCT from unrelated donors, or SCT using cord blood were associated with poor survival after allo-SCT [3,4]. Multivariate analysis in this study confirmed that male patients and patients in non-CR at SCT were at risk for poor OS. There were no differences in characteristics of the patients and SCT between male and female patients (data not shown), and the incidence of disease progression after allo-SCT was increased in male patients with marginal significance ($P = .06$). There has been no report showing worse survival in male patients after chemotherapy for ATL. It is thus tempting to speculate that this difference is due to the difference in allogeneic immune responses between male and female recipients after allo-SCT.

Although a high level of sIL-2R has been reported to reflect disease progression of ATL [13,14], the clinical significance of sIL-2R for patients who received allo-SCT remains to be determined. In this study, a high level of sIL-2R at SCT was identified as a significant risk factor for OS by univariate analysis. We did not include sIL-2R at SCT in the multivariate analysis because the level of sIL-2R at SCT was stringently correlated with disease status at SCT. However, a high level of sIL-2R at SCT was determined to be a prognostic factor when it was used as an alternative variable to disease status at SCT in multivariate analysis, and a high level of sIL-2R at SCT was a risk factor for OS in patients with non-CR at SCT, regardless of the sex of the patient. Only sIL-2R at SCT was identified as a risk factor for disease progression. Thus, sIL-2R at SCT could be a useful surrogate marker for disease status. Although transplantation outcomes in non-CR patients were inferior to those in CR patients, as has been previously reported [3,4], the level of sIL-2R at SCT was significantly associated with OS in non-CR patients, indicating that sIL-2R level at SCT could be used as a decision-making parameter for selection of allo-SCT for patients in non-CR. Additional chemotherapies or a

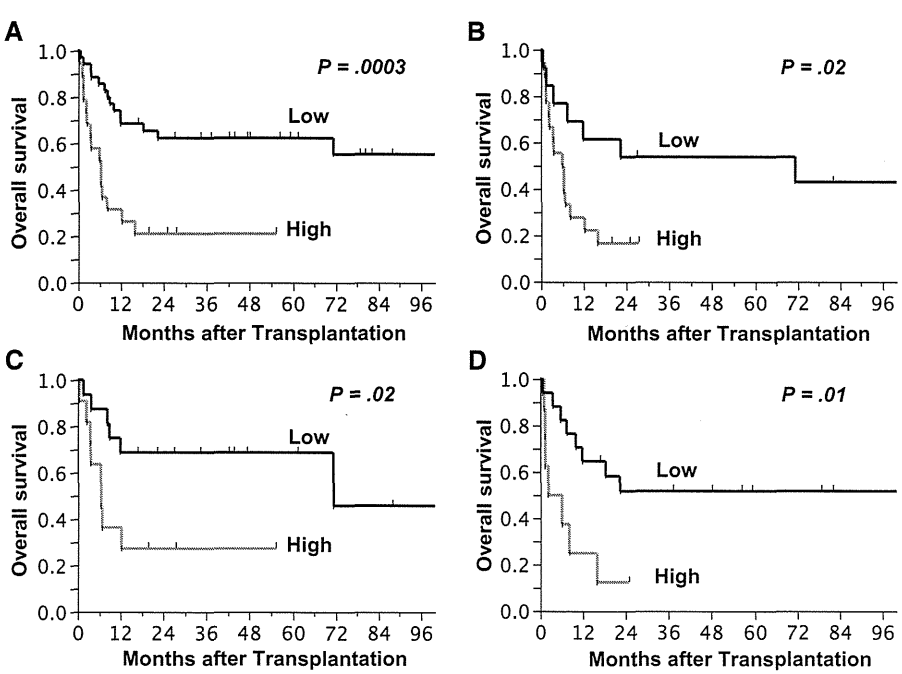

Figure 3. Overall survival according to level of serum sIL-2R at SCT. A high level of serum sIL-2R at SCT was defined as 2000 U/mL or higher. (A) All patients. (B) Patients who were in non-CR at SCT. (C) Patients with acute type of ATL. (D) Patients with lymphoma type of ATL.

novel anti-CCR4 antibody therapy [15] before SCT for patients who have high level of sIL-2R may improve the outcome of allo-SCT, although this hypothesis needs to be tested in a prospective study.

In conclusion, although the current study has several limitations that should be considered when reviewing the findings, including the use of a retrospective design and a small number of patients, it showed encouraging results of allo-SCT for patients with ATL in both CR and non-CR with low levels of sIL-2R at SCT.

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Conflict of interest statement: There are no conflicts of interest to report.

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ORIGINAL ARTICLE

Characteristic patterns of relapse after allogeneic hematopoietic SCT for adult T-cell leukemia–lymphoma: a comparative study of recurrent lesions after transplantation and chemotherapy by the Nagasaki Transplant Group

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Allogeneic hematopoietic SCT (allo-SCT) is a promising therapy that may provide long-term durable remission for adult T-cell leukemia–lymphoma (ATL) patients; however, the incidence of relapse associated with ATL remains high. To determine the clinical features of these patients at relapse, we retrospectively analyzed tumor lesions in 30 or 49 patients who relapsed following allo-SCT or chemotherapy (CHT), respectively, at three institutions in Nagasaki prefecture between 1997 and 2011. A multivariate analysis revealed that the development of abnormal lymphocytes in the peripheral blood of patients at relapse was less frequent after allo-SCT than after CHT ($P < 0.001$). Furthermore, relapse with a new lesion only in the absence of the primary lesion was more frequent in allo-SCT ($P = 0.014$). Lesions were more frequently observed in the central nervous systems of patients who relapsed with new lesions only ($P = 0.005$). Thus, the clinical manifestation of relapsed ATL was slightly complex, especially in post-transplant patients. Our results emphasized the need to develop adoptive modalities for early and accurate diagnoses of relapsed ATL.

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INTRODUCTION

Adult T-cell leukemia–lymphoma (ATL) is a peripheral T-lymphocytic neoplasm that is caused by human T-cell lymphotropic virus type I (HTLV-1).[1] One of the characteristic features of ATL is its frequent multiorgan involvement, which has been implicated in the poor prognosis of patients with ATL. Lymphadenopathy, hepatomegaly, splenomegaly, as well as skin, pulmonary and central nervous system (CNS) lesions, and 5% or more abnormal T lymphocytes in the peripheral blood have been reported in most cases of ATL. The clinical manifestation of ATL is heterogeneous and is characterized by this organ involvement, which has been used to classify the disease into four subtypes: acute, lymphoma, chronic and smoldering.[2]

ATL is resistant to various cytotoxic agents and has a poor prognosis.[3,4] Allogeneic hematopoietic SCT (allo-SCT) for patients with aggressive ATL (acute, lymphoma and the unfavorable chronic type) is considered to be a therapeutic option that can provide apparent durable remission along with graft-vs-ATL effects.[5–18] However, both the relapse rate and TRM after allo-SCT were previously shown to be high, and are urgent issues that need to be addressed.[9,19,20] Previous studies, including ours, raised the possibility that patients with local relapse may achieve long-term remission by local cytoreductive therapy alone, and that those with skin recurrence (i.e. non-aggressive disease) could benefit from DLI.[21,22] These findings implied that an intervention for the residual disease at the early phase may improve the outcomes of ATL patients; however, a standard method to monitor the residual disease after remission has not yet been established. Moreover, very few studies have examined the clinical manifestation of relapsed ATL by carefully analyzing an adequate number of cases. Identifying the clinical characteristics of ATL at relapse is important for establishing an adoptive monitoring strategy. In the present study, we retrospectively analyzed 30 and 49 ATL patients who relapsed after allo-SCT and chemotherapy (CHT), respectively, at three institutes in Nagasaki prefecture.

PATIENTS AND METHODS

Patient population

We conducted a retrospective survey of patients diagnosed with aggressive ATL[2] who received initial systemic CHT at three hospitals in Nagasaki prefecture between 1 April 1997 and 31 March 2011. The unfavorable chronic type of ATL was defined according to previous criteria.[4] The diagnosis of ATL was based on clinical features, histologically and/or cytologically proven mature T-cell malignancy, the presence of the anti-HTLV-1 Ab and the monoclonal integration of HTLV-1 original DNA into tumor cells, as described previously.[2,23,24] A total of 336 patients were excluded from the 497 patients whose data were available because they did not achieve CR after CHT or allo-SCT (Figure 1). CHT and transplant procedures were performed according to the decision of the clinicians at each center. The intrathecal administration of CHT as prophylaxis for CNS relapse was performed based on the decision of clinicians before 2007, and was then routinely performed after 2007 as described previously in a phase

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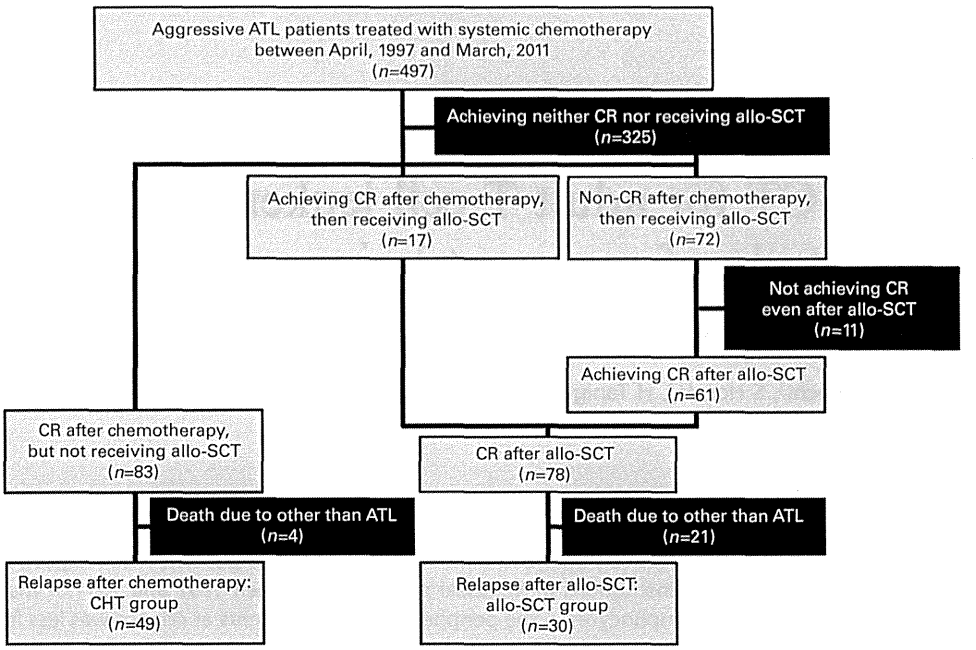

Figure 1. Patient flow diagram. We retrospectively analyzed patients who relapsed after the first CR at three institutions in Nagasaki prefecture between 1997 and 2011. Of these patients, 30 and 49 patients relapsed after allo-SCT and CHT, respectively.

III clinical trial for aggressive ATL.[4] No patient received mogamulizumab before achieving the first CR. Relapse after the first CR was observed in 79 of the remaining 161 patients, and these patients were included in this analysis. Data on the 79 patients were collected and updated as of July 2013. This study was approved by the Ethical Committee of each participating hospital.

Definitions

Performance status was based on the 5-grade scale of the Eastern Cooperative Oncology Group. Because HTLV-1 carriers frequently have a small percentage of abnormal lymphocytes with polylobated nuclei in their peripheral blood, and provided that less than 5% of such cells remained, peripheral blood involvement was confirmed if more than 5% of these abnormal lymphocytes were present in the peripheral blood.[25] The definition of extranodal lesions has been described previously.[24] Lymph nodes and extranodal tumor lesions were both determined according to the Ann Arbor classification.[2]

CR was determined according to previously described criteria.[25] The diagnosis and clinical grading of acute and chronic GVHD were performed using established criteria.[26,27]

Clinical data

We collected information regarding patient characteristics and underlying diseases (including a prognostic index for acute- and lymphoma-type ATL (ATL-PI)[28]). Factors used in analyses were listed in Table 1. The intensity of the conditioning regimen was classified as myeloablative and reduced intensity.[29] An evaluation of the involved sites was based on the Shimoyama classification.[2]

Statistics

Descriptive statistics were used to summarize variables related to patient demographic and transplant characteristics. Comparisons between the allo-SCT and CHT groups were performed using Fisher's exact test, where appropriate, for categorical variables and the Mann–Whitney *U*-test for continuous variables. The Kaplan–Meier method was used to estimate OS after relapse. The log-rank test was used in the univariate analysis in order to compare OS. The impact of potential confounding factors on the appearance of involvement sites at relapse was evaluated using Fisher's exact test and logistic regression analysis.

Leukocytosis was defined as a WBC count of 8.9×10^9/L or greater, with the median value as the cutoff level. Lactate dehydrogenase or blood urea nitrogen concentrations were dichotomized into normal and elevated concentrations.[30] Serum albumin (ALB) was dichotomized into concentrations of 40.0 g/L (4.0 g/dL) or greater and less than 40.0 g/L (4.0 g/dL).[2] Factors with at least borderline significance ($P < 0.25$) according to the univariate analysis were included in the multivariate analysis. All analyses were performed using the SAS version 9.2 software (SAS Institute, Cary, NC, USA). Values of $P < 0.05$ were considered significant in all analyses.

RESULTS

Patient characteristics and transplant procedures

Table 1 shows the patient characteristics of each group; 30 and 49 ATL patients relapsed after allo-SCT and CHT, respectively. In a total of 79 patients, the median intervals from CR to relapse and from the last treatment to relapse were 180 days (range, 28–3490) and 79 days (range, 9–3073), respectively. Intrathecal prophylaxis was not performed in 11 patients: 10 patients started the initial treatment before 2007 and 1 patient did not receive prophylaxis because of advanced age. Transplant procedures were shown in Table 2. In the allo-SCT group, nine patients achieved CR at the time of receiving allo-SCT, whereas 21 patients did not. One patient received a reduced-intensity conditioning regimen with antithymocyte globulin. No patients underwent *in vitro* T cell-depleted transplantation.

Comparison of involved sites at relapse between allo-SCT and CHT groups

The involvement sites at the initial diagnosis and relapse were shown in Table 3. At relapse, the frequency by which abnormal lymphocytes (≥5%) developed in the peripheral blood was significantly lower in the allo-SCT group than in the CHT group ($P < 0.001$). This was maintained when the percentage of abnormal lymphocytes as the threshold of peripheral blood involvement was considered to be ≥2% or ≥10% (data not shown). A multivariate analysis showed that the likelihood of developing abnormal lymphocytes in the peripheral blood at relapse was significantly lower in the allo-SCT group than in the CHT group ($P < 0.001$; Table 4). We performed a stratification analysis according to the Shimoyama classification. In patients with the acute plus unfavorable chronic type, the frequency by

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Table 1. Patient characteristics

Characteristics	*Allo-SCT group*	*CHT group*	*P-value*
No. of patients	30	49	
Median age at diagnosis, years	51 (Range, 33–65)	64 (Range, 40–83)	< 0.001
Sex, *n*			0.163
Male	13	30	
Female	17	19	
Subtype of ATL at diagnosis, *n*			0.935
Acute type	25	41	
Lymphoma type	4	7	
Unfavorable chronic type	1	1	
WBC, $\times 10^9$/L	9800 (Range, 4000–80 000)	8500 (Range, 4400–179 500)	0.959
Abnormal lymphocyte count, %	11 (Range, 0–94)	4 (Range, 0–91)	0.953
Serum ALB, g/dL	3.9 (Range, 2.6–5.4)	4.0 (Range, 2–4.6)	0.346
BUN, mg/dL	13 (Range, 7–30)	14 (Range, 5–47)	0.377
LDH, IU/mL	593 (Range, 119–1561)	451 (Range, 161-3309)	0.473
sIL-2R, U/mL	14 300 (Range, 1823–128 000)	9730 (Range, 397–114 000)	0.396
Presence of hypercalcemia, *n*			0.802
Yes	10	14	
No	20	35	
Ann Arbor stage, *n*			0.644
I–II	1	4	
III–IV	29	45	
ECOG PS, *n*			0.643
0–1	17	24	
2–4	13	25	
ATL-PI, *n*			0.273
Low score	12	10	
Intermediate score	11	26	
High score	2	5	
Unknown	5	8	
Year of initial chemotherapy, *n*			0.609
1997–2003	9	12	
2004–2010	21	37	
Initial chemotherapy, *n*			0.316
VCAP-AMP-VECP-based	24	44	
CHOP-based	6	5	
IT before CR, *n*			0.519
Yes	27	41	
No	3	8	
Interval from last treatment to relapse, day	130 (Range, 31–3073)	49 (Range, 9–2060)	0.009
Interval from CR to relapse, day	135 (Range, 31–3490)	238 (Range, 28–2060)	0.235

Abbreviations: ALB = albumin; allo-SCT = allogeneic hematopoietic SCT; ATL = adult T-cell leukemia–lymphoma; ATL-PI = a prognostic index for acute- and lymphoma-type ATL; AMP = doxorubicin, ranimustine and predonisone; BUN = blood urea nitrogen; CHOP = CY, doxorubicin, vincristine and predonisone; CHT = chemotherapy; ECOG = Eastern Cooperative Oncology Group; IT = intrathecal administration of cytarabine, MTX and predonisone; LDH = lactate dehydrogenase; PS = performance status; sIL-2R = soluble IL-2 receptor; VCAP = vincristine, CY, doxorubicin and predonisone; VECP = vindesine, etoposide, carboplatin and predonisone.

Table 2. Transplant procedure

Characteristics	*No. of patients in the allo-SCT group*
Conditioning regimen	
Myeloablative	
TBI regimen	11
Non-TBI regimen	4
Reduced intensity myeloablative	15
GVHD prophylaxis	
CYA	4
Tacrolimus	4
CYA A+sMTX	13
Tacrolimus+sMTX	9
Donor type	
HLA-matched-related donor	16
Alternative donor	14
HLA matching	
0 Mismatched loci	22
1 Mismatched locus	2
2 Mismatched loci	6
Source of stem cells	
BM	16
PBSC	7
Cord blood	7
Anti-HTLV-1 Ab of the donor	
Positive[a]	6
Negative	24
Disease status at allo-SCT	
CR	9
PR	8
Other	13
Acute GVHD	
Absent	15
Grade I	3
Grade II–IV	12
Chronic GVHD	
Absent	19
Limited type	1
Extensive type	5

Abbreviations: HTLV-1 = human T-cell lymphotropic virus type I; sMTX = short-term MTX. [a]PBMCs in these donors were subjected to southern blot analysis to examine the monoclonal integration of the HTLV-1 provirus into the genome, and all six donors were confirmed to be the carriers of HTLV-1.

which the allo-SCT group developed abnormal lymphocytes in peripheral blood at relapse was lower ($P = 0.001$ by the multivariate analysis). However, this was not clear because of the small number of patients with the lymphoma type; relapse in the peripheral blood was observed in one and three patients in the allo-SCT ($n = 4$) and CHT ($n = 7$) groups, respectively (data not shown).

Relationship between primary and relapsed lesions

We next evaluated the relationship between initially diagnosed and relapsed lesions. The most frequent lesion of relapse was the primary lesion (that is, the lesion at the initial diagnosis); 19 (63.3%) and 43 (87.8%) patients in the allo-SCT and CHT groups had primary lesions (Figure 2). Among primary involved lesions, relapse significantly occurred at the same sites: lymph nodes ($P = 0.018$), spleen ($P = 0.010$) and gastrointestinal tract ($P = 0.005$; see Supplementary Table S1). Relapse was only observed in new lesions in 11 (36.7%) and 6 (12.2%) patients in the allo-SCT and CHT groups, respectively. Lesions were more frequently observed in the CNS of patients who relapsed with new lesions only

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Table 3. Tumor lesion at the initial diagnosis and at relapse

Tumor lesion	*At the initial diagnosis* No. of patients (%)			*At relapse* No. of patients (%)		
	Allo-SCT group (n = 30)	*CHT group* (n = 49)	P-*value*	*Allo-SCT group* (n = 30)	*CHT group* (n = 49)	P-*value*
Abnormal lymphocytes (⩾5%) in the peripheral blood	16 (53.3%)	22 (44.9%)	0.495	4 (13.3%)	25 (51.0%)	< 0.001
Skin	13 (43.3%)	12 (24.5%)	0.138	9 (30.0%)	14 (28.6%)	1.000
Lung	3 (10.0%)	3 (6.1%)	0.668	3 (10.0%)	4 (8.2%)	1.000
Lymph node	21 (70.0%)	44 (89.7%)	0.035	11 (36.7%)	26 (53.1%)	0.172
Liver	6 (20.0%)	13 (26.5%)	0.595	2 (6.7%)	9 (18.7%)	0.191
Spleen	7 (23.3%)	11 (22.4%)	0.792	2 (6.7%)	10 (20.4%)	0.119
CNS	3 (10.0%)	3 (6.1%)	0.668	6 (20.0%)	7 (14.3%)	0.543
Bone	1 (3.3%)	3 (6.1%)	1.000	3 (10.0%)	3 (6.1%)	0.668
Ascites	2 (6.7%)	4 (8.2%)	1.000	1 (3.3%)	3 (6.1%)	1.000
Peripheral effusion	2 (6.7%)	5 (10.2%)	0.703	2 (6.7%)	5 (10.2%)	0.703
GI tract	3 (10.0%)	5 (10.2%)	1.000	1 (3.3%)	4 (8.2%)	0.644
Intestine	2 (6.7%)	0 (0.0%)	0.141	1 (3.3%)	0 (0.0%)	0.380

Abbreviations: allo-SCT = allogeneic hematopoietic SCT; CHT = chemotherapy; CNS = central nervous system; GI tract = gastrointestinal tract.

Table 4. Factors affecting the development of abnormal lymphocytes in the peripheral blood at relapse

Factors		*Univariate analysis*			*Multivariate analysis*		
		Odds ratio	*(95% CI)*	P-*value*	*Odds ratio*	*(95% CI)*	P-*value*
Allo-SCT	Allo-SCT group vs CHT group	0.148	0.045–0.487	< 0.001	0.095	0.025–0.364	< 0.001
Age	⩾60 vs < 60 years	2.828	1.078–7.423	0.038	—	—	—
Hypercalcemia	Presence vs absence	0.340	0.111–1.042	0.076	0.323	0.094–1.114	0.074
CNS lesion	Presence vs absence	0.116	0.006–2.140	0.080	—	—	—
Sex	Male vs female	0.433	0.170–1.101	0.102	0.236	0.075–0.747	0.014
Bulky mass	Presence vs absence	0.140	0.007–2.633	0.152	—	—	—
Interval from CR to relapse	< 180 vs ⩾180 days	0.480	0.188–1.223	0.162	—	—	—
GI tract lesion	Presence vs absence	0.219	0.026–1.882	0.246	—	—	—

Abbreviations: allo-SCT = allogeneic hematopoietic SCT; CHT = chemotherapy; CI = confidence interval; CNS = central nervous system; GI = gastrointestinal. The following factors were obtained at the initial diagnosis: age, hypercalcemia, CNS lesion, bulky mass and GI tract lesion. Factors with at least borderline significance ($P < 0.25$) according to Fisher's exact test were listed in the results of the univariate analysis.

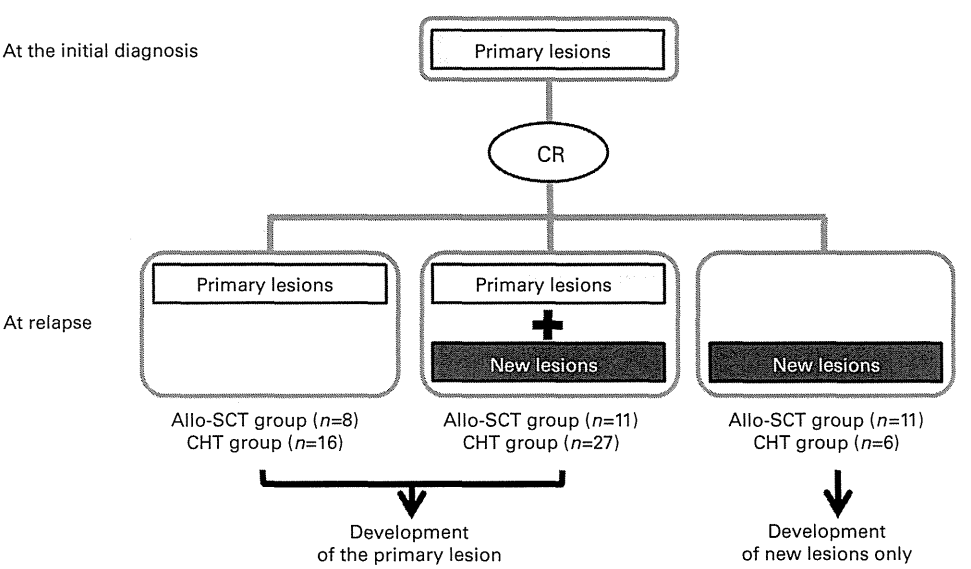

Figure 2. Relapse pattern regarding primary and new lesions. Relapse with a new lesion only was more likely to be observed in the allo-SCT group than in the CHT group ($P = 0.022$).

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Table 5. Factors affecting relapse only in new lesions

Factors		*Univariate analysis*			*Multivariate analysis*		
		Odds ratio	*95% CI*	P-*value*	*Odds ratio*	*(95% CI)*	P-*value*
Allo-SCT	Allo-SCT group vs CHT group	4.149	1.338–12.870	0.022	4.149	1.338–12.867	0.014
Lymph node lesion	Presence vs absence	0.272	0.078–0.940	0.066	—	—	—
Interval from CR to relapse	< 180 Days vs ⩾180 days	2.226	0.731–6.780	0.18	—	—	—
WBC	$\geqslant 8.9\times10^9$ vs $< 8.9\times10^9$/L	2.226	0.731–6.780	0.18	—	—	—

Abbreviations: allo-SCT = allogeneic hematopoietic SCT; CHT = chemotherapy; CI = confidence interval. The following factors were obtained at the initial diagnosis; lymph node lesion and WBC. Factors with at least borderline significance ($P < 0.25$) according to Fisher's exact test were listed in the results of the univariate analysis.

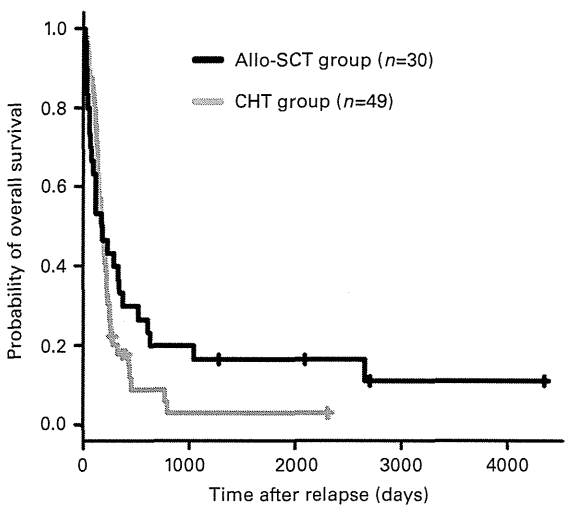

Figure 3. OS rates after relapse. The estimated OS rates after relapse were 16.7 and 3.0% at 3 years in patients who relapsed after allo-SCT and CHT, respectively.

($P = 0.005$). The relapse pattern of patients in whom new lesions only occurred at relapse was more frequently observed in the allo-SCT group than in the CHT group ($P = 0.022$). The multivariate analysis showed that the likelihood of relapse only in a new lesion was significantly higher in the allo-SCT group ($P = 0.014$; Table 5), and was also the case when patients with the acute plus unfavorable chronic type were analyzed ($P = 0.048$). We did not observe a similar result in patients with lymphoma type ATL because the number of patients was small.

We assessed the risk factors associated with CNS lesions at relapse, which was significantly observed as relapse only in a new lesion. The univariate analysis revealed that the frequency of CNS lesions at relapse was higher when ascites was detected at the initial diagnosis ($P = 0.006$), with a short CR duration ($P = 0.037$), and with a high sIL-2R value ($P = 0.024$). In the multivariate analysis, the presence of ascites at the initial diagnosis and a short CR duration were also significant ($P = 0.016$ and $P = 0.031$, respectively), whereas a high sIL-2R value was not ($P = 0.051$; see Supplementary Table S2).

Survival by the relapse pattern of ATL

The median survival times after relapse were 176 and 174 days in the allo-SCT and CHT groups, respectively (Figure 3). Estimated OS rates after relapse were 16.7% (95% confidence interval: 6.1–31.8%) and 3.0% (95% confidence interval: 0.2–12.9%) at 3 years in the allo-SCT and CHT groups, respectively. No significant differences were observed in the OS rates between the allo-SCT and CHT groups ($P = 0.198$). The OS rates were poor for patients who relapsed in pleural effusion ($P < 0.001$), ascites ($P = 0.005$) and spleen ($P = 0.002$), but was better for those who relapsed in the skin ($P = 0.031$). The OS rates of the allo-SCT and CHT groups based on the involvement sites at relapse were shown in Supplementary Tables S3 and S4.

Relationship between GVHD and the involvement site

The timing of the relapse of ATL and GVHD was shown in Supplementary Table S5. In the allo-SCT group, 11 and 13 patients relapsed after the improvement of GVHD, and without any episode of GVHD, respectively. Of the 24 patients who had no clinical symptoms of GVHD at relapse, the most frequent lesions of relapse were detected in the skin ($n = 8$) and lymph nodes ($n = 10$).

Relationship between transplant procedures and the involvement site

We evaluated the impact of conditioning regimens for the involved lesion. The univariate analysis revealed that the intensity of the conditioning regimen was not associated with any involved lesion at relapse, including the TBI 12 Gy-based regimen, or the donor type (HLA-matched sibling vs alternative donor). The development of abnormal lymphocytes in the peripheral blood correlated with the use of an unrelated donor ($P = 0.037$); of the four patients who relapsed in the peripheral blood, three and one patients underwent transplantation from unrelated BM and unrelated cord blood, respectively.

DISCUSSION

We here observed significant differences in the lesions involved in relapse after allo-SCT and CHT. To the best of our knowledge, this is the first study to evaluate the clinical features of ATL at the first relapse. It should be noted that the clinical features at relapse in the allo-SCT group were slightly more complex than those in the CHT group.

Leukemic relapse was less frequent in the allo-SCT group. Previous studies suggested that differences in extramedullary and BM relapse were attributed to the preferential occurrence of the GVL effect after transplantation for AML with stronger GVL effects in the blood system (that is, BM and peripheral blood) over extramedullary sites.[31–34] Although the underlying mechanism has not yet been elucidated in detail, an uneven graft-versus-ATL effect may explain, at least partly, the lower frequency of leukemic relapse following allo-SCT than CHT.

As we previously reported, chromosomal abnormalities and the overexpression of c-Met in ATL cells correlated with the type of involved sites at the initial diagnosis.[35,36] Considering the chromosomal instability of ATL,[37] it would be of interest to clarify the intrinsic characteristics of ATL cells that affect the pathogenesis of the involved sites at relapse.

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