Distinct clinical features of infectious complications in adult T-cell leukemia/lymphoma patients after allogeneic hematopoietic stem cell transplantation: a retrospective analysis in the Nagasaki Transplant Group

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ABSTRACT

Although allogeneic hematopoietic stem cell transplantation (allo-SCT) is performed as a curative option in adult T-cell leukemia-lymphoma (ATL) patients, its high transplantation-related mortality raises a serious issue. The clinical features of infectious complications after transplantation are not well known. To analyze the impact of infections after allo-SCT for ATL, we retrospectively compared infectious complications in 210 patients (acute myeloid leukemia (AML), n=91; acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL), n=51; ATL, n=68) at three institutes in Nagasaki prefecture between 1997 and 2009. No patient received ganciclovir/foscarvir as prophylaxis, and most patients received antifungal prophylaxis with fluconazole or itraconazole. The cumulative incidence of cytomegalovirus (CMV) infection at 3 years was 69.2% in ATL patients versus 54.4% in AML patients (p=0.0255). Cumulative infection-related mortality was significantly higher in ATL patients than that in the two other groups (ATL vs AML, p=0.0496; ATL vs ALL/LBL, p=0.0075), and most death-causing pathogens were bacteria and fungus. The appearance of CMV infection was negatively associated with infectious mortality in ATL patients, but the P-value for this association was near the borderline of significance (p=0.0569). In multivariate analysis, transplantation using unrelated bone marrow and

episodes of CMV infection were associated with worse overall survival in ATL patients, but were not in either AML or ALL/LBL patients. Collectively, the impact of infectious complications after transplantation in ATL patients was different from that in AML and ALL/LBL patients, suggesting that a more intensive strategy for infection control in ATL patients is required to reduce infectious mortality.

INTRODUCTION

Adult T-cell leukemia-lymphoma (ATL) is a peripheral T-cell neoplasm caused by human T-cell lymphotropic virus type I (HTLV-I) [1-4]. The clinical feature of ATL is heterogeneous and is characterized by various degrees of lymphadenopathy, abnormal lymphocytosis, hepatosplenomegaly, skin lesions, and hypercalcemia dividing the disease into 4 subtypes: acute, lymphoma, chronic, and smoldering [5]. Over the past decade, allogeneic hematopoietic stem cell transplantation (allo-SCT) was performed in young patients with aggressive ATL (acute, lymphoma, unfavorable chronic type) in Japan because aggressive ATL shows resistance to a variety of cytotoxic agents and has a poor outcome [6, 7]. Several reports demonstrated that allo-SCT provided apparent long-term remission in some patients, along with the graft-versus-ATL effect [8-17]. However, transplantation-related mortality (TRM) was higher than that observed for

acute leukemia (acute myeloid leukemia; AML, acute lymphoblastic leukemia/lymphoblastic lymphoma; ALL/LBL), especially within 6 months of allo-SCT [10, 14].

In general, ATL patients are susceptible to various opportunistic infections, including *Pneumocystis jirovecii* pneumonia (PJP), invasive fungal infections, and herpes virus diseases due to defective cellular immunity. Suzumiya et al. reported that cytomegalovirus (CMV) was involved in 35 of 47 autopsied cases of ATL and that CMV pneumonia was a significant cause of death [18]. Furthermore, it has been reported that development of PJP, invasive fungal infection, and herpes virus disease are more frequent in ATL patients [19-22]. Collectively, infectious complications in patients with ATL may be different from those in patients with acute leukemia or malignant lymphoma, during allo-SCT. Recently, a nationwide retrospective study in Japan pointed out that infectious mortality was a main cause of TRM after transplantation for ATL [14]. However, there are no differences in prophylaxis and treatment for infection between ATL and other hematological diseases during the allo-SCT procedure. It remains unclear whether the current strategy for infection is sufficient or not for post-transplant patients with ATL because of the lack of detailed information for infectious complications after allo-SCT in these patients.

In the present report, we retrospectively analyzed 210 post-transplant patients with ATL, AML, or ALL/LBL to clarify differences in the clinical features of infectious complications after allo-SCT for patients with ATL.

PATIENTS AND METHODS

Patient population

In this study, adult patients aged 16 years or older that received allo-SCT at 3 hospitals in Nagasaki prefecture with the diagnosis of AML, ALL/LBL, or ATL were included. These patients underwent allo-SCT between September 1997 and December 2009. Of 228 patients whose data were available, 18 were excluded because of death without neutrophil engraftment. The remaining 210 patients were included in the analysis. This study was approved by the Ethical Committees of the participating hospitals.

Definition of clinical end points and responses

Neutrophil engraftment was defined by the recovery of an absolute neutrophil count of at least 0.5×10^9/L for 3 consecutive points; platelet recovery was defined by the recovery of a count of at least 500×10^9/L without transfusion support. Diagnosis and clinical grading of acute and chronic graft-versus-host diseases (aGVHD and cGVHD)

were performed according to established criteria [23, 24].

For ATL patients, response to treatment was divided into four categories: complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Responses were defined as follows: CR, disappearance of all disease; PR, ≥50% reduction in measurable disease; SD, failure to attain CR, PR, and no PD; PD, any new lesions or lesions with proliferation (increases in the size and number of abnormal cells). For acute leukemia patients, CR was defined as the presence of all of the following: fewer than 5% blasts in bone marrow, no leukemia blasts in peripheral blood, recovery of peripheral neutrophil counts to more than 1.0×10^9/L and platelet counts to more than 100×10^9/L, and no evidence of extramedullary leukemia.

Prophylaxis of infection, and monitoring and preemptive therapy for CMV diseases

During the allo-SCT procedure, each patient was treated in a reverse isolation room, which was ventilated with a high-efficiency particulate air filtration system. As prophylaxis of fungal infection, itraconazole (200mg/day) was generally administered to most patients from the start of conditioning [25, 26]. In the cases of itraconasole intolerance due to its adverse effect, in principle, fluconazole (100mg/day) was

administered before 2004 and micafungin (50mg/day) after 2005 when micafungin became widely available for prophylaxis in Japan. If these drugs could not also be tolerated, either amphotericin B or voriconazole was administrated in accordance with the institutional strategy. Prophylaxis against PJP was performed primarily with oral trimethoprim-sulfamethoxazole (ST) [25]. All patients received prophylactic antibodies (ceftazidime or ciprofloxacin) once absolute neutrophil counts had become less than 0.5×10^9/L [25, 27]. Acyclovir (1000mg/day) was used for the prevention of diseases by the Herpes Simplex virus (HSV) and Varicella Zoster virus (VZV) until day 100 after transplantation [25, 28]. After the recovery of neutrophils, CMV pp65 antigen in peripheral blood was monitored weekly through day 100 after transplantation to detect CMV antigenemia [29]. The CMV antigenemia test was considered positive if at least one positive-stained cell per 5.0×10^4 cells was detected on the slides. Preemptive therapy was initiated when CMV antigenemia became positive. In most cases, ganciclovir (GCV) was administrated at an induction dose of 5mg/kg intravenously every 12 hours as preemptive therapy [30, 31]. After antigenemia had been eliminated, GCV was either discontinued immediately or continued for a short time at a maintenance dose, in accordance with the institutional strategy. Based on the prevalence of high positivity for CMV antibody among Japanese [32, 33], the evaluation of

CMV-serostatus before transplantation was depended on the institutional strategy. Instead, for prophylaxis of CMV, all patients received irradiated blood products which were depleted of leukocytes by filters [34]. No patient was transfused with CMV-seronegative blood components.

Fungal infections

Invasive fungal infections were divided into candidemia, invasive aspergillosis, and apparent organ damage by other fungi or molds [35]. Invasive aspergillosis was defined as possible (based on clinical signs and symptoms plus a compatible chest computed tomography scan or X-ray), probable (based on clinical signs and symptoms, compatible imaging test results, plus a positive respiratory tract culture for *Aspergillus spp* or positive galactomannan assay), and definite (based on histology for an invasive mold infection by *Aspergillus*) infections. Candida infection was defined by the positive results of fungal cultures in blood or urine samples, or by evidence of infectious lesions in any organ system demonstrated by radiographic or histological evaluation.

CMV infection and CMV disease

Diagnosis of CMV infection and CMV disease was made based on previously

described criteria [36]. In brief, CMV disease was defined by the presence of clinical signs and/or symptoms of end-organ disease combined with the detection of CMV infection in a biopsy specimen or bronchoalveolar lavage fluid in case of pneumonia. CMV infection was defined as the isolation of a virus or detection of viral protein or nucleic acids in any body fluid or tissue specimen. CMV infection included both CMV antigenemia and CMV disease.

Viral infections other than CMV

Patients who were culture- or polymerase chain reaction (PCR)-positive for adenovirus (ADV) with corresponding clinical signs and symptoms were considered to have an ADV infection involving those sites [37]. BK virus infection was defined as hemorrhagic cystitis with positive PCR results in urine samples [38], and for human herpes virus-6 (HHV-6) infection, detection of the virus genome by PCR from blood and/or cerebrospinal fluid [39].

Statistical analysis

The Kaplan–Meier method was used to estimate overall survival (OS) after allo-SCT. The 95% confidence interval of 3-year OS was calculated. To illustrate the effects of

cGVHD on OS, OS was measured from a predefined ‘landmark’ time of 100 days after allo-SCT when analyzing the effect of this factor. Probabilities between subgroups were compared by means of the log-rank test. Cumulative incidences of infectious complications and infection-related death were calculated using Gray’s method, considering deaths related to relapse or other complications than infection as a competing risk.

Furthermore, simultaneous effects of prognostic factors on OS were analyzed using multivariate regression analysis based on the Cox’s proportional hazards model and linear logistic model, respectively. Variables considered were age of the patient at transplantation, sex of the patient, donor type, disease status at conditioning, and the t(9;22) chromosome abnormality or others for ALL/LBL, cytogenetic risk group defined by the MRC group [40, 41] for AML and French-American-British (FAB) classification of M0/M6/M7 or others for AML, clinical subtypes according to criteria of the Japanese Lymphoma Study Group for ATL [5], the incidence of CMV infection, disease and antigenemia, bacterial infection, fungal infection, viral infection other than CMV, aGVHD, the conditioning regimen, and institution where patients received allo-SCT. The most appropriate models were selected based on Akaike’s information criteria (AIC). All analyses were performed using SAS version 9.2 software (SAS

Institute, Cary, NC, USA). Values of $P<0.05$ were considered significant in all analysis.

RESULTS

Patient characteristics and transplant conditions

In 228 patients who received allo-SCT in our study, 7 AML, 2 ALL/LBL, and 9 ATL patients experienced graft failure and/or rejection. The rate of graft failure and/or rejection was not statically difference among each 3 groups.

The characteristics of remaining 210 patients are shown in Table 1. All ATL and ALL/LBL patients received standard-dose chemotherapy before the procedure of transplantation, but 10 AML patients did not receive any chemotherapy before allo-SCT. Sixteen related donors for ATL patients showed a positive result for the anti-HTLV-1 antibody. Peripheral blood mononuclear cells of these donors were subjected to Southern blot analysis to examine the monoclonal integration of the HTLV-1 provirus into the genome, and all 16 donors were confirmed as carriers of HTLV-1.

ATL patients were older and were more likely to receive reduced intensity conditioning regimens than patients with AML or ALL/LBL. Reduced-intensity conditioning using anti-thymocyte globulin was administered to two ATL patients. In general, HLA matched unrelated bone marrow recipients were more likely to receive

tacrolimus-based GVHD prophylaxis than those who received allo-SCT using other stem cell sources. No patients received *in vitro* T cell-depleted transplantation. The procedure of prophylaxis for fungal infection was similar among 3 groups.

The median time to engraftment were 16 days (range, 7-29 days), 16 days (range, 10-45 days), and 16 days (range, 9-32 days) in AML, ALL/LBL, ATL groups, respectively. Acute GVHD developed in 44 AML (48.4%), 33 ALL/LBL (64.7%), and 28 ATL patients (41.2%). Severe acute GVHD (grade II-IV) was observed in 27 AML (29.7%), 24 ALL/LBL (47.1%), 23 ATL patients (33.8%). In 84 AML, 47 ALL/LBL, and 55 ATL patients who were alive for over 100 days after transplantation, chronic GVHD developed in 44 AML (52.4%), 28 ALL/LBL (59.6%), and 21 ATL patients (38.2%). Extensive chronic GVHD was observed in 29 AML (34.5%), 18 ALL/LBL (38.3%), 16 ATL patients (29.1%).

CMV antigenemia, disease, and infection

The characteristics of CMV infection (CMV antigenemia and CMV disease) are shown in Table 2. The incidence of CMV antigenemia without CMV disease in the ATL group was similar to that in AML and ALL/LBL groups. One AML patient and 3 ALL/LBL patients with CMV antigenemia improved spontaneously, but all ATL

patients received GCV and/or FCV with or without intravenous gamma globulin. CMV disease was documented in 13 out of 91 AML patients (14.3%), 9 out of 51 ALL/LBL patients (17.6%), and 15 out of 68 ATL patients (22.1%). In patients who developed CMV disease, 2 AML and 4 ATL patients developed CMV diseases despite preemptive therapy for prior CMV antigenemia. Cumulative incidence of CMV infection at 100 days and 1 year were followed; 51.7% (95% CI: 40.7-61.5%) and 54.4% (95% CI: 43.2-64.3%) in AML groups, 63.9% (95% CI: 48.5-75.8%) and 63.9% (95% CI: 48.5-75.8%) in ALL/LBL groups, and 67.5% (95% CI: 54.3-77.7%) and 69.2% (95% CI: 56.0-79.2%) in ATL groups. There was a significant difference in the cumulative incidence of CMV infection between AML and ATL groups (AML vs ATL, p=0.0255; ALL/LBL vs ATL, p=0.7011). In the patients with episodes of CMV infection, while all 32 ALL/LBL patient experienced the first CMV infection from engraftment to 100 days after allo-SCT (post-engraftment phase), 2 out of 48 AML (4.2%) and 1 out of 45 ATL patients (2.2%) experienced CMV antigenemia as first CMV infection after 100 days (late phase). In patients who experienced the improvement of CMV infection once, 12 out of 46 AML (26.1%), 11 out of 32 ALL/LBL (34.4%), and 15 out of 43 ATL patients (34.9%) developed recurrent CMV infection.

All 12 CMV-seronegative patients received transplantation form CMV-seropositive

donors. In these CMV-seronegative patients, 3 out of 7 AML and 2out of 5 ALL/LBL patients developed CMV antigenemia but not CMV disease.

Pathogens other than CMV that caused clinical infection after transplantation

Table 3 shows infectious agents other than CMV. Cumulative incidence of bacterial infection at 100 days and 1 year were followed; 13.4% (95% CI: 7.3-21.3%) and 16.0% (95% CI: 9.2-24.5%) in AML groups, 11.8% (95% CI: 4.7-22.3%) and 11.8% (95% CI: 4.7-22.3%) in ALL/LBL groups, and 20.9% (95% CI: 12.1-31.4%) and 23.0% (95% CI: 13.5-34.0%) in ATL groups. The ATL group showed the highest cumulative incidence of bacterial infection, but there was no significant difference among the three groups (data not shown). Serious bacterial infections were documented among 37 patients (sepsis, n=27; pneumonia, n=9; meningitis, n=1). Three ATL patients exhibited *Pseudomonas aeruginosa* infection (pneumonia, n=2; sepsis, n=1), but none did in AML and ALL/LBL groups.

Cumulative incidence of fungal infection at 100 days and 1 year were followed; 2.2% (95% CI: 0.4-7.0%) and 5.8% (95% CI: 2.1-12.2%) in AML groups, 2.0% (95% CI: 0.2-9.3%) and 6.4% (95% CI: 1.6-16.1%) in ALL/LBL groups, and 7.5% (95% CI: 2.7-15.5%) and 9.4% (95% CI: 3.8-18.2%) in ATL groups. The ATL group showed the

highest cumulative incidence of invasive fungal infection, without a significant difference among the three groups (data not shown). In total, 3 patients (2 ATL patients and 1 ALL/LBL patient) developed PJP without prophylactic ST, but none did in the AML group even without ST prophylaxis. Two ATL patients developed PJP with CR, respectively, at day 18 and 137 after allo-SCT. One ALL patient also developed PJP coincident with relapsed disease at day 392 after allo-SCT.

Cumulative incidence of viral infection other than CMV at 100 days and 1 year were followed; 15.9% (95% CI: 9.3-24.1%) and 29.1% (95% CI: 19.6-39.3%) in AML groups, 15.9% (95% CI: 7.4-27.3%) and 22.3% (95% CI: 11.8-34.9%) in ALL/LBL groups, and 24.5% (95% CI: 14.8-35.5%) and 33.1% (95% CI: 21.2-45.5%) in ATL groups. There was no significant difference among the three groups in the cumulative incidence of viral infections other than CMV (AML vs ALL/LBL vs ATL = 31.2% vs 25.0% vs 33.1% at 3 years) (data not shown).

Death caused by infections

Cumulative infection-related mortalities at 100 days and 1 year were followed; 2.3% (95% CI: 0.4-7.2%) and 6.1% (95% CI: 2.2-12.7%) in AML groups, 0.0% (95% CI: 0.2-9.5%) and 2.0% (95% CI: 0.2-9.5%) in ALL/LBL groups, and 9.4% (95% CI:

3.8-18.2%) and 14.7% (95% CI: 7.1-24.8%) in ATL groups. The ATL group showed the highest mortality, which was significantly greater than that of the other two groups (AML vs ATL, p=0.0496; ALL/LBL vs ATL, p=0.0075) (Figure 1a). However, in all 210 patients, ATL was not a significant factor despite the high hazard rate for infection-related mortality on multivariate analysis (Hazard rate (HR) 2.283; 95% confidence interval (CI): 0.834-6.251, p=0.1083); multivariate analysis revealed that non-remission at allo-SCT was a significant unfavorable factor for infection-related mortality (HR 2.528; 95% CI: 1.007-6.345, p=0.0482).

While non-remission at allo-SCT remained a significant risk factor for infection-related mortality in AML group, this factor did not in ALL/LBL and ATL groups. Rather, in the ATL group, infection-related mortality was higher among patients who experienced a CMV infection after allo-SCT than those who did not, but the P-value was at the borderline of significance (p=0.0569) (Figure 1b). There was no significant relationship between episodes of CMV infection and mortality caused by infection in either the AML or ALL/LBL group (AML group, p=0.3160; ALL/LBL group, p=0.4461). Additionally, to exclude the bias due to the CMV-serostatus of patients, infection-related mortalities were analyzed in patients with CMV-seropositive of each 3 groups. For CMV-seropositive patients, the comparison of cumulative

infection-related mortalities between those with episodes of CMV infection and without showed a significant difference in ATL group; the episodes of CMV infection have a significant negative impact on infection-related mortalities in the ATL group (p=0.0492), but not in the AML and ALL/LBL groups (p=0.0840 and p=0.4276, respectively).

The difference of institution did not have any impact on the cumulative infection-related mortalities in each 3 groups. In ATL group, the HTLV-1 serostatus of donor was not associated with cumulative infection-related mortalities.

The pathogens resulting in fatal infectious complications are shown in Table 4. Interestingly, despite the high incidence of CMV infection after allo-SCT, only 4 patients died of CMV diseases (CMV pneumonia in 2 ATL and 2 AML patients), and no ALL/LBL patient died of any CMV disease. Of these 4 patients, one AML and one ATL patients died of recurrent CMV infection on late phase. In the patients who died of infection on late phase, 4 out of 6 ATL, 1 out of 4 AML and no ALL/LBL patients died of bacterial infection. The proportion of bacteria in the pathogens resulting in fatal infectious complications on late phase after allo-SCT was likely to be higher in ATL group than in each AML and ALL/LBL groups, but this difference was not significant. The pathogens inducing fatal complications in 4 ATL patients on late phase were either methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*, which were

resistant to many antibiotic agents. Also, these 4 ATL patients experienced the improvement of CMV antigenemia by GCV on post-engraftment phase (ie. before the development of fatal bacterial infections).

Survival

The outcomes of allo-SCT in each 3 groups are shown in Table 5. Median survival times after allo-SCT were 4.0 years and 1.0 year in the AML group and ATL group, respectively. Median survival was not reached in the ALL/LBL group (Figure 2a). Estimated OS after transplantation were 49.9% (95% CI: 38.2-60.5%), 58.3% (95% CI: 41.2-71.9%), and 34.9% (95% CI: 23.2-46.8%) at 5 years in AML, ALL/LBL, and ATL groups, respectively. OS for ATL patients was significantly worse than that for AML ($p=0.0089$) and ALL/LBL groups ($p=0.0023$), while OS rates for AML and ALL/LBL patients were similar ($p=0.2982$).

Univariate analysis for survival

Univariate analysis for survival identified several pretransplantation and posttransplantation factors. The disease status (CR or PR) at transplantation had a significant positive impact in both AML ($p<0.0001$) and ALL/LBL groups ($p=0.0050$),

but not in the ATL group. The existence of aGVHD (grade II-IV) was associated with worse survival in the AML group (p=0.0007). AML patients with cGVHD (extensive type) (p=0.0302) and ATL with cGVHD (limited type) (p=0.0140) showed a better OS than without cGVHD. Episode of fungal infection provided a negative impact on OS for AML (p=0.0015) and ALL/LBL groups (p=0.0459). Episodes of bacterial infection (p=0.0102) and CMV infection (p=0.0184) had a significant negative impact in the ATL group (Figure 2b, c). In CMV-seropositive patients of each 3 groups, episode of CMV infection negatively affected survival with a borderline difference in the ATL groups (p=0.0615), but there was no relationship in the AML and ALL/LBL groups (p=0.4680 and p=0.4620, respectively).

There was no significant relationship between the difference of institution and OS in each 3 groups. For the ATL group, neither the use of anti-thymocyte globulin in the conditioning regimen nor the HTLV-1 serostatus of donor was associated with survival.

Multivariate analysis for survival

Multivariate analysis in all 210 patients revealed 6 factors that adversely affected OS: ATL (HR 1.944; 95% CI: 1.204-3.141, p=0.0066), older age (HR 2.204; 95% CI 1.364-3.562, p=0.0012), non-remission (HR 3.153; 95% CI 2.041-4.868, p<0.0001),

bacterial infection (HR 2.121; 95% CI 1.267-3.550, p=0.0042), fungal infection (HR 2.718; 95% CI 1.507-4.901, p=0.0009), and myeloabrative conditioning (HR 2.064; 95% CI 1.149-3.707, p=0.0154).

To clarify the distinct unfavorable features in ATL groups, we also performed multivariate analysis for survival respectively in each 3 groups (Table 6). There were 4 factors that adversely affected OS in the AML group: patient age (≥ 42 years; HR 2.283; 95% CI: 1.164-4.476, p=0.0163), lack of CR at transplantation (HR 2.975; 95% CI: 1.285-6.888, p=0.0109), the existence of aGVHD (grade II-IV) (HR 1.731; 95% CI: 1.327-2.258, p<0.0001), and episodes of fungal infection (HR 3.934; 95% CI: 1.357-11.406, p=0.0117). In the ALL/LBL group, two factors were associated with worse survival: lack of CR at transplantation (HR 3.874; 95% CI: 1.481-10.134, p=0.0058) and episodes of fungal infection (HR 3.430; 95% CI: 1.029-11.435, p=0.0448). In the ATL group, two factors that differed from those in the AML or ALL/LBL group had a negative impact on OS with significance: the use of unrelated bone marrow (HR 2.568; 95% CI: 1.127-5.854, p=0.0248) and episodes of CMV infection (HR 2.514; 95% CI: 1.178-5.366, p=0.0171). Although the difference of institution was analyzed in multivariate analysis as a factor, this difference was not selected as a factor in each 3 groups.

DISCUSSION

The success or failure of allo-SCT is mostly determined in the first 6 months after allo-SCT. Outcome closely correlates with the reconstitution of donor cell derived immunity, which affects the survival of recipients through GVHD and the graft-versus-leukemia effect, and the degree of immune competence achieved against infectious agents. Recently, some reports have indicated that the incidence of fungal infection and CMV infection has increased after engraftment, particularly among patients with severe immunodeficiency. For example, after allo-SCT using *in vitro* or *in vivo* T-cell depletion, fungal infection, and reactivation of the Epstein-Barr virus and CMV are closely related to serious complications [42-49]. Also, the risk of infectious complications, including HHV-6 encephalitis and CMV diseases, is higher in patients who received cord blood transplantation [42, 50-54]. These results suggested that the incidence of infectious complications depends not only on infectious disease-causing pathogens but also on the background of the patient or the cause of immunosuppression.

In our study, while the cumulative incidence of either bacterial or fungal infection was similar among the three groups, the ATL group showed the highest cumulative incidence of infection-related death, mainly caused by these infections. Importantly, bacteria

resistant to many antibiotic agents emerged as a cause of death after 100 days in ATL patients. It is suggested that ATL patients after allo-SCT would be more susceptible to life-threatening bacterial infections even on late phase than those with acute leukemia, and that the current strategy for infection would not be sufficient for allo-SCT to ATL. Hence, it seems that the development of an adoptive strategy in post-transplant patients with ATL is required.

The appearance of a CMV infection showed a negative impact for OS as an independent variable in the ATL group. Interestingly, while there were only 2 ATL patients having CMV disease at the time of death, the risk of infectious death in ATL patients who experienced CMV infection (that included CMV antigenemia) was likely to be higher. Namely, episodes of CMV infection could predict a higher risk of death caused by not only CMV disease, but also other infections, which may help to identify the ATL patients that should receive more intensive management for infection.

It is not clear why episodes of CMV infection correlated with the outcome of ATL patients, although multivariate analysis identified episodes of CMV infection as an independent variable only in the ATL group. It has been shown that episodes of CMV infection were associated with a worse outcome in post-transplant patients with defective cellular immunity [43, 44, 55]. Therefore, it is speculated that persistent

compromised cellular immunity after transplantation led to the higher susceptibility of CMV and other infections among ATL patients, resulting in worse outcomes than leukemia patients. Considering that the reactivation of CMV itself and the prolonged administration of GCV were thought to induce greater immune suppression [56, 57], we hypothesize that the direct and indirect influence of CMV infection adversely promoted immunosuppression attendant on ATL patients. It remains to be elucidated how immunologic recovery was delayed after transplantation in ATL patients. Since the immune system recovery following allo-SCT was not sufficiently evaluated in our study, the monitoring of immune function after transplant, such as analysis of lymphocyte subset and quantitative estimation of immunoglobulin, should be considered in a future study.

It is possible that CMV-serostatus affected the result of statistical analysis in our study, because CMV-serostatus, which was unexamined in 37.6% patients, was not included in the statistical analysis. Therefore, to remove the bias of this point, the analysis for ATL patients with CMV-seropositive revealed that CMV infection was also identified as a risk factor in infection-related mortality and OS. Considering that it has been reported that about 90% Japanese showed CMV-seropositive, the difference of CMV-serostatus would not have a big impact in our study. However, a larger analysis for matched

patient’s background regarding with CMV-serostatus would help to confirm our findings.

ATL group showed that the highest cumulative incidence of infection-related mortality and the various pathogens causing death, indicating that it was difficult to establish the uniform management to reduce the fetal infectious complications for post-transplant patients with ATL. However, it is speculated that more intensive management for bacterial infection might provide the reduction of infection-related death in some post-transplant patients with ATL, since ATL group would be more likely to show the higher risk of fetal antibiotic-resistant bacterial infection even on late phase in our study. Therefore, appropriate antibiotic treatment using prolonged bacterial surveillance culture should be considered, particularly in ATL patients with persistent compromised cellular immunity. Moreover, because of a limitation of treatment active on multi-drug resistant gram negative rods, particularly *Pseudomonas aeruginosa*, at the present situation, the introduction of new treatment options, including antibiotic combination therapy using a “break-point checker board plate” and developing antibiotic agents such as colistin [58-62], are expected in patients who developed such infection after allo-SCT.

Our results showed the higher risk of fetal infectious complications in post-transplant

patients with ATL. However, the number of patients is limited and the detailed treatment protocols were not completely uniform. Thus, it is possible that these factors exerted a bias and affected results: for instance, the small number of patients in our study resulted in wide and overlapping confidence intervals despite P values <0.05. Out finding should be interpreted carefully, and they should be confirmed in larger prospective studies.

In conclusion, we found that the clinical features of infectious complications after allo-SCT in ATL patients are different from those in AML and ALL/LBL patients. Because allo-SCT offers the best chance of prolonged survival by inducing graft-versus-ATL effect, developing supportive care to minimize fatal infectious complications would be important, in particular, for post-transplant patients with ATL. Our data suggested that ATL patients require more intensive management for infections according to individualized risk such as the appearance of CMV infection. Such a strategy may be beneficial in reducing TRM in post-transplant patients with ATL.

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Figure 1. Cumulative incidence of infection-related death after transplantation

Cumulative incidence of infection-related death after transplantation: (a) Infectious mortality was higher in the ATL group than that in the two other groups; (b) In the ATL group, infectious mortalities were higher in ATL patients with episodes of CMV infection than in those without, but the P-value for this association was near the borderline of significance. The 95% confidence intervals at 1, 3, 5, and 10 years were shown in each infection-related mortality.

Figure 2. Overall survival after transplantation

Kaplan-Meier estimate of overall survival (OS) after transplantation: (a) OS of the

ATL group was significantly worse than that of either the AML or ALL/LBL group; (b) In ATL group, the OS of ATL patients with episodes of CMV infection was significantly worse than those without; (c) In the ATL group, the OS of ATL patients with episodes of bacterial infection was significantly worse than those without. The 95% confidence intervals at 1, 3, 5, and 10 years were shown in each OS.

Table 1. Patient Characteristics

	AML	ALL/LBL	ATL
No. of patients	91	51	68
Median age at allo-SCT (range)	42 (17-70)	32 (16-60)	51 (30-67)
Sex (male/female)	41/50	21/30	42/26
Disease classification			
AML (French-America-British)			
M0	6		
M1	9		
M2	36		
M3	5		
M4	19		
M5	6		
M6	7		
M7	1		
Others	2		
AML cytogenetic risk group*			
Favorable	18		
Intermediate	46		
Adverse	21		
Unknown	6		
ALL cytogenetic			
t(9;22)		17	
Normal		13	
Others		17	
Unknown		4	
ATL subtype			
Acute			50
Lymphoma			17
Chronic			1
Disease status at allo-SCT			
CR	39	38	15
PR	-	-	21
Relapse/Induction failure	42	13	32
Untreated	10	0	0
Donor			
HLA-matched related donor	46	21	37
Alternative donor	45	30	31
HLA matching			
0 mismatched loci	73	35	47
1 mismatched locus	5	7	6
2 mismatched locus	13	9	15
Source of stem cells			
Bone marrow	56	31	30
Peripheral blood stem cell	23	14	20
Cord blood	12	6	18
Conditioning regimen			
Myeloabrative	74	45	32
Reduced-intensity Myeloabrative	17	6	36
GVHD prophylaxis			
Cyclosporine A + sMTX	45	22	33
Cyclosporine A ± others	3	1	10
Tacrolimus + sMTX	31	25	15
Tacrolimus ± others	12	3	10
Prophylaxis for fungal infection			
Itraconazole	51	29	40
Fluconazole	22	12	20
Micafungin	13	7	5
Voriconazole	3	1	3
Amphotericin	2	2	0
Acute GVHD			
Grade 0	47	18	40
Grade I	17	9	5
Grade II-IV	27	24	23
Chronic GVHD			
Absent	40	19	34
Limited type	15	10	5
Extensive type	29	18	16
Anti-HTLV-1 antibody of donor			

Positive	0	0	16
Negative	91	51	52
CMV serostatus of recipient			
Positive	52	30	37
Negative	7	5	0
Unknown	32	16	31

AML, indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma; ATL, adult T-cell leukemia/lymphoma; allo-SCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; PR, partial remission; sMTX, short-term methotrexate; GVHD, graft versus host disease; and CMV, cytomegalovirus.

* Based on the karyotype of leukemia cells, patients were classified into either the favorable, intermediate, or adverse risk group, defined by the MRC group.

Table 2. CMV infection

	AML (n=91)		ALL/LBL (n=51)		ATL (n=68)	
CMV infection						
Antigenemia without CMV disease	36	(39.6%)	23	(45.1%)	30	(44.1%)
Pneumonia	5	(5.5%)	3	(5.9%)	8	(11.8%)
Gastroenteritis	7	(7.7%)	3	(5.9%)	4	(5.9%)
Hepatitis	0		3	(5.9%)	0	
Pneumonia and Gastritis	1	(1.1%)	0		2	(2.9%)
Gastroenteritis and Hepatitis	0		0		1	(1.5%)

Table 3. Infectious agents other than CMV

	Pathogen	Pre-engraftment (days 0 to engraftment)	Post-engraftment (engraftment to days +100)	Late phase (days 100 to >365)
AML group (n=91)	Bacteria	Gram-positive organism (n=4) Gram-negative organism (n=2)	Gram-positive organism (n=6)	Gram-positive organism (n=3) Gram-negative organism (n=1)
	Fungus	*Aspergillus spp* (n=1)	*Aspergillus spp* (n=1)	*Candida spp* (n=2) *Aspergillus spp* (n=2)
	Virus*	none	*Human herpes virus 6* (n=5) *Adenovirus* (n=1) *Herpes simplex virus* (n=3) *Varicella zoster virus* (n=2) *BK virus* (n=2) *Epstein-Barr virus* (n=1)	*Human herpes virus 6* (n=1) *Adenovirus* (n=1) *Herpes simplex virus* (n=1) *Varicella zoster virus* (n=7) *Epstein-Barr virus* (n=1)
ALL/LBL group (n=51)	Bacteria	Gram-positive organism (n=3)	Gram-positive organism (n=1)	none
	Fungus	none	*Candida spp* (n=1)	*Mucor spp* (n=1) *Aspergillus spp* (n=2) *Pneumocystic jirovecii* (n=1)
	Virus*	*BK virus* (n=1)	*Human herpes virus 6* (n=3) *Adenovirus* (n=3) *Herpes simplex virus* (n=1) *Influenza virus* (n=1)	*Varicella zoster virus* (n=4)
ATL group (n=68)	Bacteria	Gram-positive organism (n=6) Gram-negative organism (n=5)	Gram-positive organism (n=1) Gram-negative organism (n=3)	Gram-positive organism (n=3) Gram-negative organism (n=2)
	Fungus	*Aspergillus spp* (n=1)	*Candida spp* (n=2) *Aspergillus spp* (n=3)	*Aspergillus spp* (n=2) *Pneumocystic jirovecii* (n=1)
	Virus*	*Human herpes virus 6* (n=2) *Adenovirus* (n=1) *BK virus* (n=2)	*Human herpes virus 6* (n=2) *Adenovirus* (n=5) *Varicella zoster virus* (n=3) *BK virus* (n=1)	*Herpes simplex virus* (n=1) *Varicella zoster virus* (n=3)

* Virus did not include CMV infection.

Table 4. Agents of infection-related death

	Post-engraftment phase (engraftment to days +100)	Late phase (days 100 to >365)
AML group (n=91)	*MRSA* (n=1) *Enterococcus spp* (n=1) *Aspergillus spp* (n=1) *Cytomegarovirus* (n=1)	*Escherichia coli* (n=1) *Candida spp* (n=2) *Cytomegarovirus* (n=1)
ALL/LBL group (n=51)	none	*Adenovirus* (n=1)
ATL group (n=68)	*Enterococcus spp* (n=1) *Stenotrophomonas maltophilia* (n=1) *Pneumocystis jirovecii* (n=1) *Human herpes virus-6* (n=1) *Adenovirus* (n=1) *Cytomegarovirus* (n=1)	*MRSA* (n=1) *Pseudomonas aeruginosa* (n=3) *Pneumocystis jirovecii* (n=1) *Cytomegarovirus* (n=1)

MRSA indicates methicillin-resistant *Staphylococcus aureus.*

Table 5. Transplantation outcome

	AML (n=91)	ALL/LBL (n=51)	ATL (n=68)
Alive/dead	48/43	33/18	25/43
Cause of death			
Bacterial infection	3	-	6
Fungal infection	3	-	2
CMV disease	2	-	2
Viral infection other than CMV	-	1	2
Disease progression	24	12	21
GVHD with or without any infection	5	2	4
Bleeding	1	-	2
Organ failure without any infection	5	3	3
Secondary malignancy	-	-	1

Table 6. Multivariate analysis of risk factors for overall survival

	AML		ALL/LBL		ATL	
	P-value	Hazard ratio	P-value	Hazard ratio	P-value	Hazard ratio
Age ≥ median age	p=0.0163	2.283	not selected		p=0.3487	1.363
without CR or PR at allo-SCT	p=0.0109	2.975	p=0.0058	3.874	not selected	
aGVHD (grade II -IV)	p<0.0001	1.731	not selected		not selected	
Unrelated BM	not selected		not selected		p=0.0248	2.568
Cord blood	not selected		not selected		p=0.8645	0.936
CMV infection	not selected		not selected		p=0.0171	2.514
Invasive fungal infection	p=0.0117	3.934	p=0.0448	3.430	not selected	

In the ATL group, episodes of CMV infection significantly correlated with worse OS. However, there was no such association in either the AML or ALL/LBL group.

Figure 1. Cumulative incidence of infection-related death after transplantation

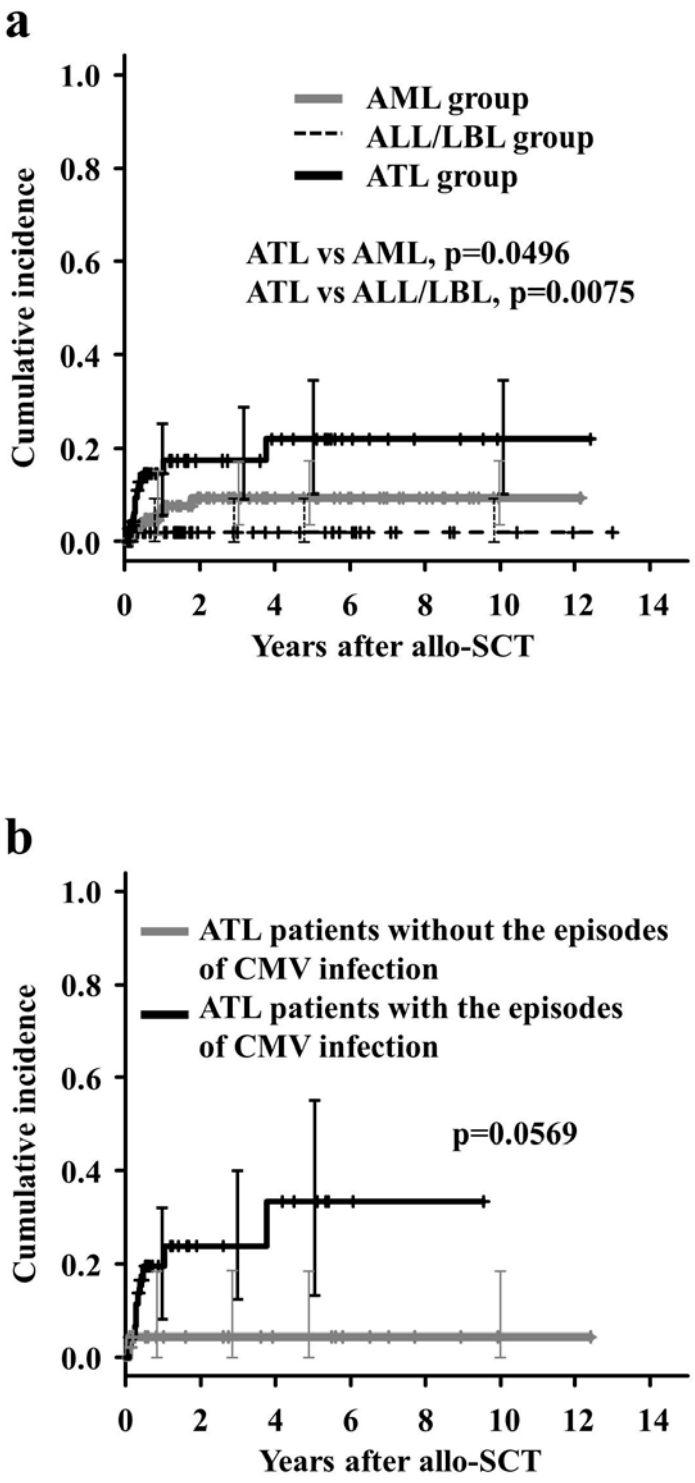
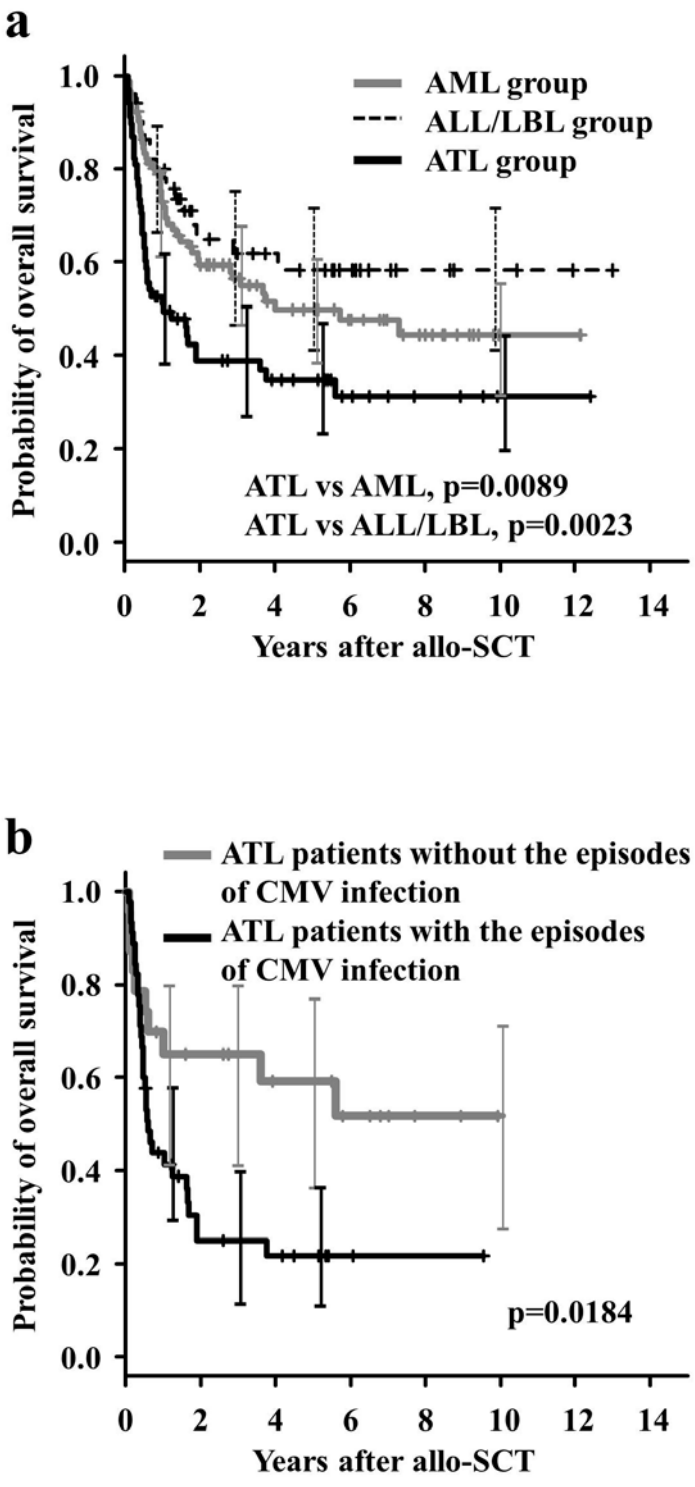
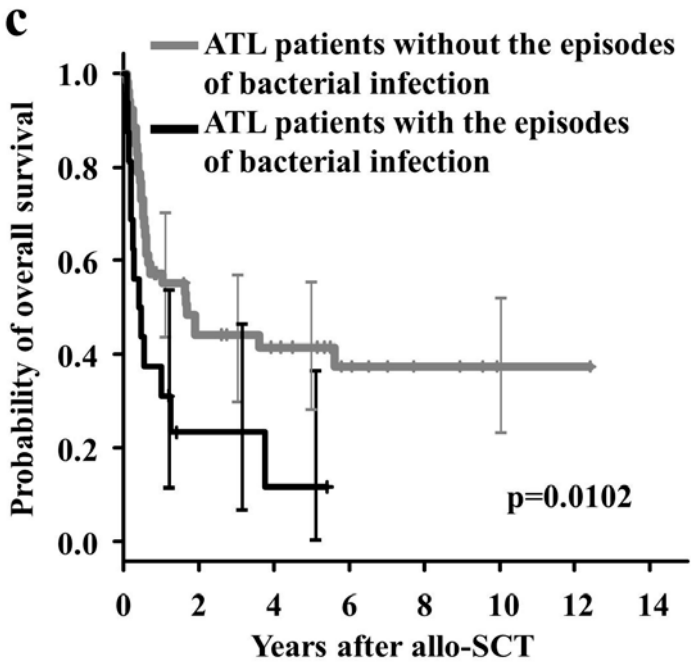


Figure 2. Overall survival after transplantation

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ATL patients without the episodes of bacterial infection
ATL patients with the episodes of bacterial infection
Probability of overall survival
1.0
0.8
0.6
0.4
0.2
0.0
p=0.0102
0
2
4
6
8
10
12
14
Years after allo-SCT