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Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study

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Adult T-cell leukemia-lymphoma (ATL) is an intractable mature T-cell neoplasm. We performed a nationwide retrospective study of allogeneic hematopoietic stem cell transplantation (HSCT) for ATL in Japan, with special emphasis on the effects of the preconditioning regimen. This is the largest study of ATL patients receiving HSCT. Median overall survival (OS) and 3-year OS of bone marrow or peripheral blood transplantation recipients (n = 586) was 9.9 months (95% confidence interval, 7.4-13.2 months) and 36% (32%-41%), respectively. These values for recipients of myeloablative conditioning (MAC; n = 280) and reduced intensity conditioning (RIC; n = 306) were 9.5 months (6.7-18.0 months) and 39% (33%-45%) and 10.0 months (7.2-14.0 months) and 34% (29%-40%), respectively. Multivariate analysis demonstrated 5 significant variables contributing to poorer OS, namely, older age, male sex, not in complete remission, poor performance status, and transplantation from unrelated donors. Although no significant difference in OS between MAC and RIC was observed, there was a trend indicating that RIC contributed to better OS in older patients. Regarding mortality, RIC was significantly associated with ATL-related mortality compared with MAC. In conclusion, allogeneic HSCT not only with MAC but also with RIC is an effective treatment resulting in long-term survival in selected patients with ATL. (*Blood.* 2012;120(8):1734-1741)

Introduction

Adult T-cell leukemia-lymphoma (ATL) is an aggressive peripheral T-cell neoplasm caused by human T-cell lymphotropic/leukemia virus type-1. It has a very poor prognosis.[1-4] A recent phase 3 trial for previously untreated patients with aggressive ATL (acute, lymphoma, or unfavorable chronic type) aged 33 to 69 years demonstrated that the dose-intensified multidrug regimen VCAP-AMP-VECP resulted in a median overall survival (OS) and OS at 3 years of 12.7 months and 24%, respectively. The OS plot for this treatment did not reach a plateau.[5] Alternatively, based on a meta-analysis, Bazarbachi et al proposed that zidovudine (AZT) and interferon (IFN)–α should be considered the standard for first-line therapy in patients with acute, chronic, or smoldering types of ATL. They reported median OS and 5-year OS for acute-type ATL treated with AZT/IFN-α to be 9 months and 28%, respectively, whereas these values were 7% and 0%, respectively, for lymphoma-type ATL.[6] These results indicate that conventional chemotherapeutic agents alone, even including AZT/IFN-α, yield few or no long-term remissions or potential cures in ATL patients.

Although early experience in myeloablative chemoradiotherapy together with autologous hematopoietic stem cell rescue for ATL was associated with a high incidence of relapse and fatal toxicities,[7] allogeneic hematopoietic stem cell transplantation (HSCT) has been explored as a promising alternative treatment that can provide long-term remission in a proportion of patients with ATL.[8-10] Therefore, we previously performed a nationwide retrospective study of ATL patients who received allogeneic HSCT in Japan before December 31, 2005, with special emphasis on the effect of the graft source: 296 patients received bone marrow (BM) and/or peripheral blood stem cells (PBSCs) and 90 received cord blood.[11] We concluded that allogeneic HSCT using currently available sources is an effective treatment in selected patients with ATL, although greater effort is warranted to reduce treatment-related

Submitted March 9, 2012; accepted June 4, 2012. Prepublished online as *Blood* First Edition paper, June 11, 2012; DOI 10.1182/blood-2012-03-414490.

There is an Inside *Blood* commentary on this article in this issue.

The online version of the article contains a data supplement.

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mortality (TRM). In addition, the use of unrelated cord blood as a stem cell source was associated with lower survival, with a median OS and unadjusted 3-year probability of OS of 2.6 months and 17% (95% confidence interval [CI], 9%-25%), respectively. Because the results suggested that allogeneic BM and PBSCs could be considered to be the more standard donor forms, rather than unrelated cord blood, for transplantation in ATL, as a next step, here we report results of a nationwide retrospective study of Japanese ATL patients receiving allogeneic HSCT, especially focusing on bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT), with special emphasis on the effects of the preconditioning regimen. Our current analysis included the previous cohort[11] (January 1996–December 2005) with updated clinical information as well as data on one patient who received allogeneic HSCT in February 1992 and patients who received allogeneic HSCT after December 2005. It is thought that allogeneic HSCT with reduced intensity conditioning (RIC) depends more on donor cellular immune effects after transplantation and less on the cytotoxic effects of the conditioning regimen to eradicate residual tumor cells than conventional myeloablative conditioning (MAC). In this context, RIC might be suitable for ATL because several reports have suggested the existence of graft-versus-T-cell lymphotropic/leukemia virus type-1 or graft-versus-ATL effects.[12-18] In addition, RIC might be associated with reduced TRM, which has represented a significant obstacle to successful allogeneic HSCT for ATL patients.[11] Furthermore, ATL has a long latency and occurs in older individuals at a median age of nearly 60 years.[19,20] There is the possibility that HSCT with RIC can provide clinical benefits for those older patients who hardly benefit from allogeneic HSCT with MAC. Here, we performed multivariate analyses of OS and treatment-related or ATL-related mortality after allogeneic BMT and PBSCT and have identified factors influencing transplantation outcomes in ATL patients.

Methods

Collection of data

Data on patients with ATL who had received their first allogeneic BMT, PBSCT, or BMT + PBSCT between February 1992 and December 2009 were collected from nationwide survey data of the Japan Society for Hematopoietic Cell Transplantation (JSHCT). Cases with missing preconditioning or survival data were excluded, with the result that 586 patients were included in the analysis. Data collected for analysis included the patients' clinical characteristics such as age at transplantation, sex, disease status at transplantation, date of transplantation, time from ATL diagnosis to transplantation, performance status (PS) according to the Eastern Cooperative Oncology Group criteria at transplantation, source of stem cells, relationship between recipient and donor, ATL clinical subtype,[1] preconditioning regimens, date alive at last follow up, date and cause of death, and incidence and severity of acute graft-versus-host disease (GVHD). When serologic or molecular typing for HLA-A, HLA-B, and HLA-DR were identical between the recipient and the related donor, we determined the relationship as HLA-matched related. As a control, data on patients with ATL who had received their first unrelated cord blood transplantation (CBT) between March 2001 and December 2009 were collected from the nationwide survey data of the JSHCT. Cases with missing survival data were excluded, resulting in the inclusion of 174 patients in the present study. The study was approved by the data management committees of the JSHCT, as well as by the institutional ethics committee of Nagoya City University Graduate School of Medical Sciences.

Definitions

OS was defined as the time from transplantation until death, and patients who remained alive at the time of the last follow-up were censored. For analysis, patients were divided into 2 age groups, either $>$ or $\leq$ 55 years, because the Japanese Clinical Oncology Group is currently conducting a phase 2 study of strategies including allogeneic HSCT other than CBT with MAC for ATL patients aged 20 to 55 years (UMIN000004147). Reported causes of death were reviewed and categorized into ATL-related or TRM. ATL-related mortality was defined as death caused by relapse or progression of ATL in patients who survived for at least 1.0 month after transplantation based on the judgment of each institution. TRM was defined as any death other than ATL-related mortality. Acute GVHD was diagnosed and graded using traditional criteria[21] by the physicians who performed transplantations at each institution. Patients undergoing allogeneic BMT or PBSCT were divided into 2 groups based on the preconditioning regimens, with 1 group being MAC and the other group RIC. MAC or RIC was defined according to the proposals by Giralt et al[22] and Bacigalupo et al,[23] with a slight modification. In the present study, MAC was defined as any regimen that includes (1) $\geq$ 5 Gy of total body irradiation (TBI) as a single fraction or $\geq$ 8 Gy fractionated, (2) busulfan (BU) $>$ 8 mg/kg orally or the intravenous equivalent, or (3) melphalan (Mel) $>$ 140 mg/m^2. All other regimens were classified as RIC. MAC was further subdivided into 4 groups as follows: TBI (n = 208), BU (n = 46), Mel (n = 21), and other types (n = 3). RIC also was subdivided into 3 groups: fludarabine (Flu) + BU (n = 165), Flu + Mel (n = 86), and other types (n = 49).

Statistical analysis

Descriptive statistics were used for summarizing variables related to patient demographics and transplant characteristics. Comparisons among the groups were performed by Fisher exact test as appropriate for categorical variables. The probability of OS was estimated according to the Kaplan-Meier method. The Cox proportional hazard model was used for multivariate analyses for OS using all independent variables in the model and then using a stepwise selection method by minimizing the Akaike Information Criterion (AIC). The AIC penalizes overparametrization, and variables are retained only when the model improves enough to balance the number of parameters. The lower the AIC, the better the predictive model fits the data.[24] Our inspection of plots of OS estimates versus follow-up time indicated that the assumption of proportional hazards for all variables used seemed to be valid. In the Cox proportional hazard model, incidence and severity of acute GVHD was treated as a time-varying covariate[25] as described previously.[12] Fine and Gray proportional hazard modeling was used to estimate the effect of the same variables used in multivariate analysis of OS on the cumulative incidence of TRM and ATL-related mortality, respectively.[26,27] All analyses including competing risk analysis[28,29] were performed using the cmprsk package of R Version 2.9.0 for Windows statistics software. Statistical significance was set at $P < .05$.

Results

Patients' characteristics

Among 586 ATL patients who received allogeneic BMT or PBSCT (mean age, 52 years; median, 53 years; range, 15-72 years), 280 received MAC (mean age, 48 years, median, 49 years; range, 15-69 years) and the remaining 306 received RIC (mean age, 56 years; median, 57 years; range, 28-72 years). Characteristics of these ATL patients are shown in Table 1. In comparison with MAC recipients, significantly more RIC recipients belonged to the older age group (56-72 years), more often received PBSCs as the stem cell source and more frequently had a related donor transplantation. There was no significant difference between MAC and RIC recipients regarding PS distribution from 0 to 4, but unknown PS was observed in significantly more MAC recipients than RIC recipients. There were no significant differences between MAC and

Table 1. Characteristics of ATL patients receiving allogeneic HSCT

Characteristic	MAC	RIC	*P*
Total patients, no. (%)	280	306	
Age range at transplantation, y			< .001
15-55	248 (89)	124 (41)	
56-72	32 (11)	182 (59)	
Sex			.135
Female	120 (43)	151 (49)	
Male	160 (57)	155 (51)	
Disease status at transplantation			.206
CR	96 (34)	112 (37)	
Non-CR	160 (57)	179 (58)	
Unknown	24 (9)	15 (5)	
Year.month of transplantation			.473
1992.2-2004.12	71 (25)	78 (25)	
2005.1-2006.11	69 (25)	77 (25)	
2006.11-2008.5	76 (27)	68 (22)	
2008.5-2009.12	64 (23)	83 (27)	
Time from diagnosis to transplantation, mo			.569
0.5-4.9	74 (26)	72 (24)	
4.9-6.9	66 (24)	79 (26)	
6.9-10.1	74 (26)	71 (23)	
≥10.1	65 (23)	81 (26)	
PS at transplantation			.004
0	102 (36)	119 (39)	
1	121 (43)	143 (47)	
2	29 (10)	25 (8)	
3	4 (1)	12 (4)	
4	3 (1)	2 (1)	
Unknown	21 (8)	5 (2)	
Source of stem cells			< .001
BM	212 (76)	186 (60)	
Peripheral blood	68 (24)	118 (39)	
BM + peripheral blood	0 (0)	2 (1)	
Relationship between recipient and donor			.019
HLA-matched related	96 (34)	117 (38)	
HLA-mismatched related	21 (8)	42 (14)	
HLA-unknown related	1 (0)	1 (0)	
Unrelated	162 (58)	146 (48)	
ATL clinical subtype			.253
Chronic, smoldering	10 (4)	6 (2)	
Acute	163 (58)	170 (56)	
Lymphoma	79 (28)	87 (28)	
Unknown	28 (10)	43 (14)	

RIC recipients regarding sex, disease status at transplantation (in complete remission [CR], not in CR, or unknown), and ATL clinical subtypes (chronic/smoldering, acute, lymphoma, or unknown). There were also no significant differences between MAC and RIC recipients regarding the date of transplantation and time from diagnosis to transplantation, both of which were equally distributed in quartiles among the 586 cases.

The 174 ATL patients who received unrelated CBT were aged 54 years, on average, with a median of 55 years and range of 27 to 79 years. There were 69 females and 105 males, with an ATL status at transplantation of CR (n = 50), not in CR (n = 115), and unknown (n = 9).

As for infectious complications, 145 of the 280 MAC recipients had bacterial infection, and 94 did not. Information on bacterial infection was missing for the remaining 41 MAC recipients. As for fungal infection, 23 and 219, respectively, did and did not have fungal infection; no such information was available on 38 patients. As to viral infection, 65 and 177, respectively, did and did not experience a viral infection, with such data missing on the remaining 38 patients. When we examined data on infectious complications in the RIC recipients, we found that of the 306 RIC recipients 134 had bacterial infection and 121 did not, with data unavailable for the remaining 51 patients. Twenty-three RIC recipients had fungal infection and 232 did not; no such information was available for 51 patients. As to viral infection, 57 and 199 patients, respectively, had and did not have viral infection; no information was available on the remaining 50 patients.

OS of patients receiving allogeneic HSCT

The unadjusted 3-year probability of OS was 36% (95% CI, 32%-41%) in the 586 ATL patients receiving allogeneic BMT or PBSCT and 21% (95% CI, 15%-29%) in the 174 patients receiving unrelated CBT. The median OS of the former was 9.9 months (95% CI, 7.4-13.2 months) and of the latter, 4.3 months (95% CI, 3.2-6.5 months; Figure 1A).

The unadjusted 3-year probability of OS was 39% (95% CI, 33%-45%) in the 280 ATL patients receiving MAC and 34% (95% CI, 29%-40%) in the 306 patients receiving RIC. The median OS of the former was 9.5 months (95% CI, 6.7-18.0 months), and of the latter 10.0 months (95% CI, 7.2-14.0 months; Figure 1B).

Multivariate analysis of factors influencing OS in ATL patients receiving allogeneic BMT or PBSCT

Of the 586 ATL patients receiving allogeneic HSCT other than unrelated CBT, 4 were excluded because of lack of data on the time from diagnosis to transplantation, 2 were excluded because of receiving BMT and PBSCT together, and 2 were excluded because of lack of data on HLA. Multivariate analysis of OS was therefore conducted on a total of 578 patients (Table 2). The following 10 variables were analyzed: age (15-55 or 56-72 years), sex, disease status (CR, not CR, or unknown), date of transplantation (1992.2-2004.12, 2004.12-2006.10, 2006.10-2008.4, or 2008.4-2009.12), time

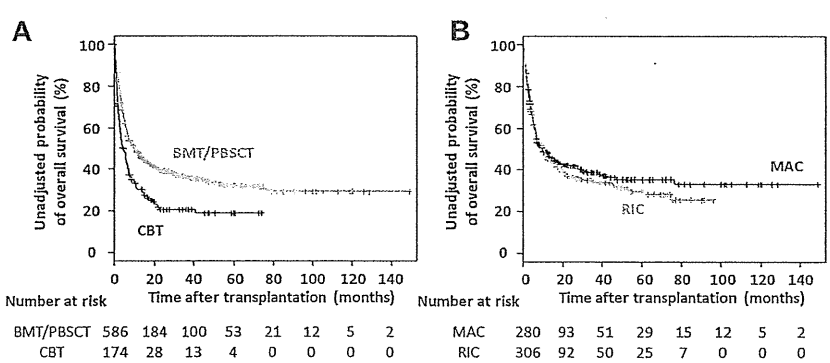

Figure 1. OS of ATL patients receiving allogeneic HSCT. (A) Kaplan-Meier curves of estimated OS in ATL patients receiving allogeneic BMT, PBSCT, or unrelated CBT. (B) Kaplan-Meier curves of estimated OS in ATL patients receiving allogeneic BMT or PBSCT with MAC or RIC.

Table 2. Multivariate analysis of factors influencing OS in ATL patients receiving allogeneic HSCT

Variable	No.	HR	95% CI	P
Age range at transplantation, y				
15-55	368	1.000		Reference
56-72	210	1.334	(1.035-1.719)	.026
Sex				
Female	267	1.000		Reference
Male	311	1.376	(1.113-1.702)	.003
Disease status at transplantation				
CR	205	1.000		Reference
Non-CR	335	1.940	(1.511-2.490)	< .001
Unknown	38	1.744	(1.114-2.731)	.015
PS				
0	219	1.000		Reference
1	260	1.498	(1.171-1.916)	.001
2-4	74	4.057	(2.957-5.565)	< .001
Unknown	25	1.489	(0.863-2.570)	.153
Relationship between recipient and donor				
HLA-matched related	210	1.000		Reference
HLA-mismatched related	62	1.296	(0.917-1.831)	.142
Unrelated	306	1.276	(1.009-1.613)	.042
Preconditioning regimen				
MAC	278	1.000		Reference
RIC	300	1.087	(0.845-1.398)	.515

from diagnosis to transplantation (0.5-4.9, 4.9-6.9, 6.9-10.1, or 10.1-143.2 months), PS (0, 1, 2-4, or unknown), source of stem cells (BM or PBSCs), relationship between recipient and donor (HLA-matched related, HLA-mismatched related, or unrelated), ATL clinical subtype (chronic/smoldering, acute, lymphoma, or unknown), and preconditioning regimen (MAC or RIC). Five variables, age, sex, disease status, PS, and relationship between recipient and donor, were retained by stepwise Cox regression analysis by minimizing the AIC, as was the preconditioning regimen, which received special emphasis in this study. Of these 6 variables, the following 5 significantly affected OS: older age (56-72 years compared with 15-55 years; hazard ratio [HR], 1.334; 95% CI, 1.035-1.719), male sex (HR, 1.376; 95% CI, 1.113-1.702), not being in CR compared with CR (HR, 1.940; 95% CI, 1.511-2.490), worse PS (1 compared with 0; HR, 1.498; 95% CI, 1.171-1.916, 2-4 compared with 0; HR, 4.057; 95% CI, 2.957-5.565), and transplantation from an unrelated donor compared with HLA-matched related donor (HR 1.276; 95% CI, 1.009-1.613).

Multivariate analysis of factors influencing OS including acute GVHD in ATL patients receiving allogeneic BMT or PBSCT

Of the 586 ATL patients receiving allogeneic HSCT other than unrelated CBT, 2 were excluded because of lack of data on HLA and 57 were excluded because of missing any data on the time from transplantation to onset of acute GVHD or the severity of acute GVHD. Thus, multivariate analysis on 527 ATL patients was performed using the following 7 variables: age, sex, disease status, PS, relationship of the donor to the recipient, preconditioning regimen, and incidence and severity of acute GVHD. Of these, 5 variables significantly affected OS; they were male sex (HR, 1.472; 95% CI, 1.168-1.855), not in CR (HR, 1.943; 95% CI, 1.491-2.532), worse PS (1 compared with 0; HR, 1.534; 95% CI, 1.182-1.991, 2-4 compared with 0; HR, 3.223; 95% CI, 2.256-4.605), transplantation from an unrelated donor compared with that from an HLA-matched related donor (HR, 1.449; 95% CI, 1.115-1.882), and acute GVHD. HRs for death of recipients having grades 1 or 2 and 3 or 4 acute GVHD compared with recipients having no acute GVHD were 0.753 (95% CI, 0.576-0.984), and 1.538 (95% CI, 1.123-2.107), respectively (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). This result suggesting that an appropriate level of acute GVHD contributed to better OS but that severe GVHD contributed to inferior OS was consistent with our previous report.[12] In contrast, the inclusion of a posttransplant time-varying covariate, acute GVHD, into the present study resulted in a decrease in the number of evaluable patients. In addition, the inclusion of patients who died so early after transplantation that onset of acute GVHD would not yet have occurred provided unacceptable bias leading to the finding that recipients without acute GVHD had worse OS compared with recipients with acute GVHD. Thus, we conducted the present subsequent analyses that aimed to clarify the significance of the preconditioning regimen MAC versus RIC in ATL patients by only including time-fixed covariates that were present pretransplantation.

Interactions of the preconditioning regimen with age, disease status, and PS for OS

Statistical interactions between the preconditioning regimens and age, disease status, or PS at transplantation for OS were tested by adding an interaction term into the multivariate analysis that included the following 6 variables: age, sex, disease status,

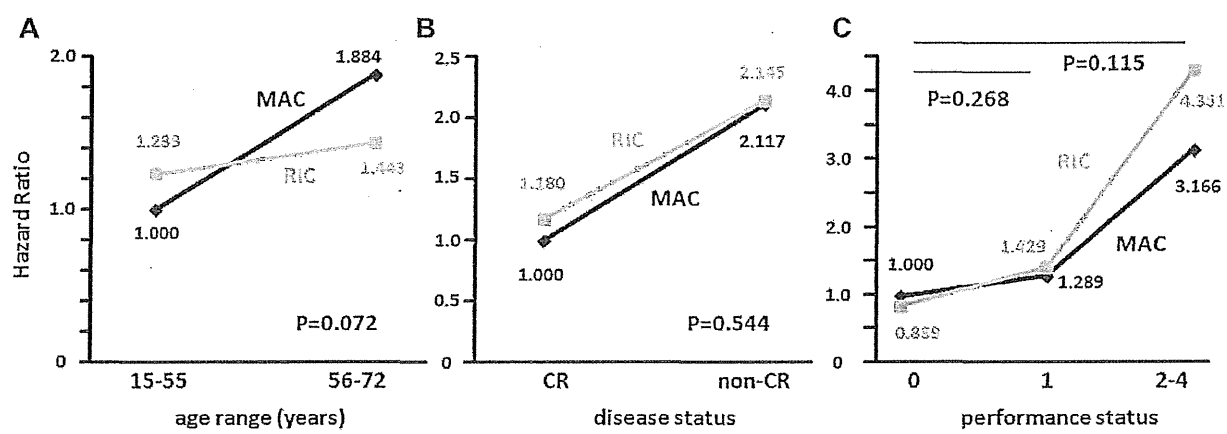

Figure 2. Interactions of the preconditioning regimen with age, disease status, and performance status for OS. Statistical interactions between the preconditioning regimens (MAC or RIC) and age range (15-55 vs 56-72 years; A), disease status (CR vs non-CR; B), and performance status (0 vs 1 or 2-4; C) were analyzed.

Table 3. Multivariate analysis of factors influencing OS in the subgroup of ATL patients receiving transplantation after MAC

Variable	No.	HR	95% CI	P
Age range at transplantation, y				
15-55	246	1.000		Reference
56-72	32	1.667	(1.051-2.643)	.030
Sex				
Female	120	1.000		Reference
Male	158	1.458	(1.053-2.019)	.023
Disease status at transplantation				
CR	95	1.000		Reference
Non-CR	159	2.071	(1.409-3.043)	< .001
Unknown	24	1.536	(0.822-2.870)	.178
PS				
0	102	1.000		Reference
1	120	1.322	(0.909-1.922)	.144
2-4	36	3.073	(1.920-4.919)	< .001
Unknown	20	1.109	(0.565-2.175)	.764
Relationship between recipient and donor				
HLA-matched related	96	1.000		Reference
HLA-mismatched related	21	1.165	(0.618-2.196)	.637
Unrelated	161	1.323	(0.920-1.902)	.131
Type of MAC				
TBI-based	208	1.000		Reference
BU-based	46	0.757	(0.475-1.206)	.242
Mel-based	21	1.388	(0.819-2.353)	.223
Others	3	0.666	(0.158-2.817)	.581

PS, relationship of the donor to the recipient, and preconditioning regimen. Among the 578 patients for whom multivariate analysis for OS was conducted (Table 2), when the HR for death of MAC recipients of a younger age (15-55 years) was determined as 1.000, the HRs of MAC recipients in the older age group (56-72 years) and RIC recipients in the younger and older age groups were 1.884, 1.239, and 1.443, respectively ($P_{interaction} = 0.072$; Figure 2A). When the HR for death of MAC recipients with CR at transplantation was determined as 1.000, HRs of MAC recipients with non-CR and RIC recipients with CR and non-CR were 2.117, 1.180, and 2.145, respectively ($P_{interaction} = 0.544$; Figure 2B). When the HR for death of MAC recipients with PS 0 at transplantation was determined as 1.000, HRs of MAC recipients with PS 1 and RIC recipients with PS 0 and 1 were 1.289, 0.839, and 1.429, respectively ($P_{interaction} = 0.268$), and HRs of MAC and RIC recipients with PS 2 to 4 were 3.166 and 4.351, respectively ($P_{interaction} = 0.115$; Figure 2C).

Multivariate analysis of factors influencing OS in the subgroup of ATL patients who had transplantation after MAC

Of the 280 ATL patients who received MAC, 1 patient was excluded because of missing data on the time from diagnosis to transplantation and one was excluded because of lack of data on HLA. Multivariate analysis was therefore conducted on 278 patients and included the variables of age, sex, disease status, PS, and relationship of the donor to recipient, which were found to have significantly affected OS in the entire subject population (Table 2). Also included was a sixth variable, the type of MAC (TBI, BU, Mel-based, or others). Of these 6 variables, 4 significantly affected OS, namely, older age (HR, 1.667; 95% CI, 1.051-2.643), male sex (HR, 1.458; 95% CI, 1.053-2.019), not in CR (HR, 2.071; 95% CI, 1.409-3.043), and worse PS (2-4 compared with 0; HR, 3.073; 95% CI, 1.920-4.919; Table 3).

Multivariate analysis of factors influencing OS in the subgroup of patients receiving transplantations after RIC

Of the 306 ATL patients receiving RIC, 3 were excluded because of lack of data on the time from diagnosis to transplantation, 2 were excluded because of receiving BMT and PBSCT together, and 1 was excluded because of lack of data on HLA. Thus, multivariate analysis on 300 ATL patients was performed using the following 6 variables: age, sex, disease status, PS, relationship of the donor to the recipient, and type of RIC (Flu + BU, Flu + Mel-based, or others). Of these, 4 significantly affected OS, namely, male sex (HR, 1.475; 95% CI, 1.100-1.978), not in CR (HR, 1.743; 95% CI, 1.249-2.432), worse PS (1 compared with 0; HR, 1.803; 95% CI, 1.293-2.516, 2-4 compared with 0; HR, 6.175; 95% CI, 3.908-9.756), and type of RIC (Flu + Mel compared with Flu + BU based; HR, 0.645; 95% CI, 0.453-0.918; Table 4).

Multivariate analysis of TRM and ATL-related mortality

Among the 586 ATL patients receiving allogeneic BMT or PBSCT, 14 could not be assigned to either the TRM or ATL-related mortality category because detailed information regarding cause of death was missing. The Fine and Gray proportional hazards model was applied to the remaining 572 patients to identify variables affecting TRM and ATL-related mortality, respectively. The variables included age, sex, disease status, PS, and relationship between recipient and donor, which was shown to significant affect OS in the entire patient population (Table 2), and the preconditioning regimen, namely, MAC or RIC. Among these variables, sex and PS were significantly associated with TRM. The HR for TRM of male patients was 1.383 (95% CI, 1.026-1.863). HRs for TRM of recipients with PS 1 and PS 2 to 4 compared with PS 0 were 1.509 (95% CI, 1.075-2.118) and 3.004 (95% CI, 1.915-4.714), respectively. Conversely, disease status, PS, and the preconditioning regimen were significantly associated with ATL-related mortality. HR for ATL-related mortality of recipients not in CR was

Table 4. Multivariate analysis of factors influencing OS in the subgroup of patients receiving transplantation after RIC

Variable	No.	HR	95% CI	P
Age range at transplantation, y				
15-55	122	1.000		Reference
56-72	178	1.127	(0.834-1.523)	.435
Sex				
Female	147	1.000		Reference
Male	153	1.475	(1.100-1.978)	.009
Disease status at transplantation				
CR	110	1.000		Reference
Non-CR	176	1.743	(1.249-2.432)	.001
Unknown	14	1.959	(0.998-3.843)	.051
PS				
0	117	1.000		Reference
1	140	1.803	(1.293-2.516)	< .001
2-4	38	6.175	(3.908-9.756)	< .001
Unknown	5	4.979	(1.849-13.409)	.001
Relationship between recipient and donor				
HLA-matched related	114	1.000		Reference
HLA-mismatched related	41	1.279	(0.836-1.959)	.257
Unrelated	145	1.237	(0.895-1.710)	.198
Type of RIC				
Flu + BU-based	165	1.000		Reference
Flu + Mel-based	86	0.645	(0.453-0.918)	.015
Others	49	0.854	(0.557-1.310)	.470

Table 5. Multivariate analysis of TRM and ATL-related mortalities in patients receiving allogeneic HSCT

	TRM				ATL-related mortality			
Variable	No.	HR	95% CI	*P*	No.	HR	95% CI	*P*
Age range at transplantation, y								
15-55	116/362	1.000		Reference	93/362	1.000		Reference
56-72	79/210	1.403	(0.954-2.064)	.085	62/210	0.955	(0.658-1.385)	.810
Sex								
Female	75/262	1.000		Reference	66/262	1.000		Reference
Male	120/310	1.383	(1.026-1.863)	.033	89/310	1.226	(0.886-1.697)	.220
Disease status at transplantation								
CR	58/205	1.000		Reference	32/205	1.000		Reference
Non-CR	121/330	1.238	(0.906-1.691)	0.180	114/330	2.203	(1.469-3.302)	< .001
Unknown	16/37	1.507	(0.873-2.603)	0.140	9/37	1.511	(0.663-3.444)	.330
PS								
0	54/213	1.000		Reference	44/213	1.000		Reference
1	91/260	1.509	(1.075-2.118)	.017	74/260	1.272	(0.872-1.856)	.210
2-4	41/75	3.004	(1.915-4.714)	< .001	30/75	1.679	(1.035-2.723)	.036
Unknown	9/24	1.214	(0.614-2.403)	0.580	7/24	1.965	(0.802-4.818)	.140
Relationship between recipient and donor								
HLA-matched related	62/206	1.000		Reference	60/206	1.000		Reference
HLA-mismatched related	18/62	0.924	(0.532-1.606)	0.780	26/62	1.392	(0.873-2.220)	.160
Unrelated	115/304	1.429	(1.033-1.975)	.031	69/304	0.843	(0.589-1.209)	.350
Preconditioning regimen								
MAC	100/274	1.000		Reference	61/275	1.000		Reference
RIC	95/298	0.786	(0.538-1.148)	0.210	94/304	1.579	(1.080-2.308)	.019

2.203 (1.469-3.302). The HR for ATL-related mortality of recipients with PS 2 to 4 compared with PS 0 was 1.679 (95% CI, 1.035-2.723), and the HR of patients receiving RIC compared with MAC was 1.579 (95% CI, 1.080-2.308; Table 5).

Cumulative incidence of TRM and ATL-related mortality

Among the 572 ATL patients receiving allogeneic BMT or PBSCT, the cumulative incidence of TRM one year after transplantation was 32.7% (95% CI, 27.1-38.4) in MAC recipients and 29.2% (95% CI, 24.0-34.5) in RIC recipients. These figures at 3 years were 37.7% (95% CI, 31.8-43.6) and 33.3% (95% CI, 27.7-38.9), respectively (Figure 3). The cumulative incidence of ATL-related mortality 1 year after transplantation was 18.5% (95% CI, 14.1-23.4) for MAC and 25.0% (95% CI, 20.1-30.1) for RIC recipients and was 22.5% (95% CI, 17.5-27.9) and 33.2% (95% CI, 27.6-38.9), respectively, at 3 years (Figure 3).

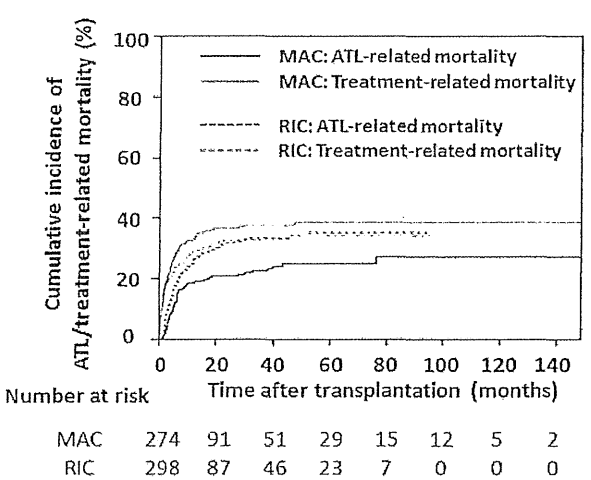

Figure 3. Cumulative incidence of ATL-related and TRMs in patients receiving BMT or PBSCT. Probabilities of ATL-related and TRMs in recipients of MAC or RIC were estimated using cumulative incidence curves to accommodate competing events.

Discussion

To the best of our knowledge, the present study is the largest retrospective study of ATL patients receiving allogeneic HSCT. Results showed that for allogeneic BMT or PBSCT for ATL, RIC was applied more frequently in older patients, as is reasonable and expected. RIC patients more often received PBSCT and had related donors. We surmise this was because RIC was initially proposed in the setting of PBSCT from HLA-matched sibling donors.[30]

The OS plot of ATL patients receiving allogeneic HSCT reached a plateau, leading to long-term survival of a subgroup of ATL patients. Recipients of CBT had a significantly worse prognosis than recipients of BMT or PBSCT, which was consistent with our previous report.[11] Direct comparison of transplantation outcomes between unrelated CBT and the other types of allogeneic HSCT was not possible because the selection of the graft source is an individual process strongly influenced by donor availability and the patient's ATL status. However, even considering such potential biases, the outcome of unrelated CBT seems clearly unsatisfactory. Thus, novel strategies to further improve the outcomes of unrelated CBT are warranted.

Among ATL patients receiving allogeneic BMT or PBSCT, multivariate analysis revealed 5 significant independent variables affecting OS, namely, age, sex, disease status, PS, and relationship between the recipient and donor. Of these factors, younger age, good ATL disease status, and PS at transplantation contributing to better OS were to be expected. The contribution to a better OS of HSCT from HLA-A, -B, and -DR–matched related donors also would be expected. The reason why the female sex was an independent favorable factor is not fully understood but is consistent with results of our previous study.[11] With respect to preconditioning, there was no significant difference in OS between MAC

and RIC recipients. To further clarify the clinical significance of preconditioning in allogeneic BMT or PBSCT for ATL, we analyzed the interactions of preconditioning with age, disease status, and PS. There was a clear trend indicating that RIC contributed to better OS in older patients compared with MAC. In contrast, the associations between MAC and RIC to OS were almost similar even if ATL patients at transplantation were in CR or not. In general, when considering allogeneic HSCT for many other types of leukemia/lymphoma patients who are in non-CR, it seems more usual to apply MAC for those patients because MAC should have the more potent effect in eradicating residual leukemia/lymphoma cells than RIC. However, the present study does not support this strategy at least in HSCT for ATL. The associations between MAC and RIC to OS were almost similar even when the PS at transplantation was 0, 1, or 2 to 4. In general, considering allogeneic HSCT for patients who have a worse PS, it seems to be more usual to apply RIC because RIC should be less toxic for recipients than MAC. However, the present study also does not support this strategy, at least in HSCT for ATL.

In the subgroup analyses stratified by MAC or RIC, older age was an independent unfavorable prognostic factor in MAC recipients, but not in RIC recipients. Female sex, good ATL disease status, and PS significantly contributed to better OS in both groups. Among MAC recipients, there was no significant difference in OS according to the type of MAC, but among RIC recipients, a Flu + Mel–based regimen contributed to better OS compared with a Flu + BU–based regimen. Although RIC regimens that contain alemutuzumab have been widely used in various parts of the world,[31] we had no data available as to whether any of the regimens used included alemtuzumab. Thus, we were not able to clarify the significance of the inclusion of alemtuzumab as a conditioning agent.

Multivariate analysis of variables contributing to mortality demonstrated that there was significantly more ATL-related mortality in RIC recipients. Although not statistically significant, a clear trend showed an association of increased TRM but not ATL-related mortality in older patients. Male sex was significantly associated with increased TRM, which might contribute to the better OS of female recipients. ATL patients not in CR had greater ATL-related mortality, but not TRM. A poor PS was significantly associated with both ATL-related mortality and TRM, but the association was closer with TRM. HSCT from unrelated donors was significantly associated with increased TRM but not with ATL-related mortality.

Cumulative incidence curves of TRM and ATL-related mortalities in MAC and RIC recipients showed characteristic features as illustrated in Figure 3. In comparison with the black lines indicating ATL-related mortality, the red lines showing TRM rise in the early phase after transplantation. Two solid lines for MAC had quite different trajectories, with TRM being greater than ATL-related mortality at any time after transplantation. In contrast, the 2 dotted lines for RIC nearly joined at 24 months after transplantation and were almost identical thereafter. Both lines for RIC were between those for MAC TRM and ATL-related mortality.

Currently, several promising new agents for ATL are being developed.[32-35] These novel treatments should increase the number of ATL patients with a sufficient disease control status and who have maintained a good PS who could become suitable candidates for transplantation. This would require further improvement in allogeneic HSCT for ATL as well as better rescue strategies for patients relapsing after HSCT. Although treatment by AZT/IFN-α[6] and/or alemutuzumab[34,36] are applied for ATL patients in many countries, none of these agents are currently approved in Japan for the treatment of ATL under the national health insurance. Therefore, there are currently no data on their clinical impact on outcome after allogeneic HSCT for ATL. We do expect, however, that the application of AZT/IFN and alemutuzumab would contribute to improved outcomes of HSCT for ATL.

Although this study reports significant novel findings for allogeneic HSCT for ATL patients, it also has inherent limitations common among observational retrospective studies. Eligibility for transplantation as well as choice of transplantation protocol, including the selection of MAC or RIC, was determined by the physicians at each institution. Regarding mortality analysis, it is not easy to determine whether death of an ATL patient after allogeneic HSCT is TRM or ATL-related mortality. This is partially because relapsed ATL patients sometimes achieve partial or complete remission on decreasing or discontinuing immunosuppressive agents, donor lymphocyte infusions, or chemotherapy, which can result in long-term remission and survival.[9,13,18]

In conclusion, allogeneic BMT or PBSCT not only with conventional MAC but also RIC is an effective treatment that results in long-term survival of selected patients with ATL. Posttransplantation outcomes are influenced by the recipient's age, sex, PS, disease status at transplantation, and the relationship between recipient and donor. Although no significant difference in OS between MAC and RIC recipients was observed, there was a clear trend that RIC contributed to better OS in older patients. Regarding results of analysis of mortality, RIC was more significantly associated with ATL-related mortality in comparison with MAC. More definitive conclusions on the role of allogeneic HSCT in the therapeutic algorithm for ATL will need to be drawn from well-designed prospective clinical trials.

Acknowledgments

The authors are grateful to all the physicians and data managers at the institutes who contributed valuable data on transplantation for ATL to the JSHCT. The authors thank all the members of the data management committees of JSHCT and Prof Sadao Suzuki (Department of Public Health, Nagoya City University Graduate School of Medical Sciences) for valuable advice on the statistical analyses.

This work was supported by a Grant-in-Aid for Scientific Research (H22-Clinical Cancer Research-general-028; T.I. and A.U.) from the Ministry of Health, Labor, and Welfare, Japan.

Authorship

Contribution: T.I., M.H., K.K., R.T., and A.U. designed the research, organized the project, and wrote the paper; T.I. and T.N. performed statistical analysis; H.S. and R.S. collected data from JSHCT; Y.M. collected data from JMDP; K.K. collected data from JCBBN; and all authors interpreted data, reviewed, and approved the final manuscript.

Conflict-of-interest disclosure: Nagoya City University Graduate School of Medical Sciences has received research grant support from Kyowa Hakko Kirin for works provided by T.I. The remaining authors declare no competing financial interest.

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特集 悪性リンパ腫の薬物療法最前線

4．非ホジキンリンパ腫に対する組織型別薬物療法の実際—3）T/NK細胞性リンパ腫に対する薬物療法—（3）超高悪性度T細胞性リンパ腫に対する薬物療法

①成人T細胞白血病/リンパ腫

石塚賢治*

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View Points !

▶病型分類を行い，aggressive ATLかindolent ATLかを見極め，直ちに治療を開始するべきかどうかを決定する。

▶ATLの治療成績はまだまだ改善の必要があり，臨床試験に組み入れることを積極的に検討する。

▶臨床試験外では，aggressive ATLに対しては強力な化学療法を開始し，可能な症例では骨髄破壊的あるいは非破壊的造血幹細胞移植を計画する。

▶臨床試験外では，indolent ATLに対しては無治療経過観察，必要に応じて皮膚病変等への局所治療を行う。

病型を決定し，直ちに治療を行うべきかどうかを見極める

- 成人T細胞白血病/リンパ腫（ATL）は4病型に分けられる[1]（表1）。治療方針を決定するためにはこの病型分類が欠かせない。さらに慢性型は，①LDHが施設正常値上限を超える，②BUNが施設正常値上限を超える，③血清アルブミンが施設正常値下限を下回る，のいずれかを持つ予後不良因子を有する慢性型と，いずれも持たない予後不良因子を有さない慢性型に分けられる[2]。
- 本邦での治療方針[3]

①Aggressive ATL：急性型，リンパ腫型，予後不良因子を有する慢性型
- 強力な化学療法
- 70歳以下では，造血幹細胞移植（骨髄破壊的，あるいは骨髄非破壊的）を考慮する。

②Indolent ATL：予後不良因子を有さない慢性型，くすぶり型
- Aggressive ATLに移行（急性転化）するまで無治療経過観察（watch and wait）
- 皮膚病変に対する局所療法

Aggressive ATLに対する一次治療は？

- 多数例での前向き臨床試験が実施されているのは，VCAP－AMP－VECP（ビンクリスチン（VCR）＋シクロホスファミド（CPA）＋ドキソルビシン（DXR）＋プレドニゾロン（PSL）－DXR＋ラニムスチン（MCNU）＋PSL－ビンデシン（VDS）＋エトポシド（ETP）＋カルボプラチン（CBDCA）＋PSL）療法とCHOP（VCR＋CPA＋DXR＋PSL）

表1 ATLの臨床病型

	くすぶり型	慢性型	リンパ腫型	急性型
抗HTLV-I抗体	＋	＋	＋	＋
リンパ球（$\times 10^9$/L）	＜4	≧4	＜4	＊
異常Tリンパ球	≧5％	＋[b]	≦1％	＋[a]
T細胞マーカーを持つ花細胞	時々	時々	No	＋
LDH	≦1.5N	≦2N	＊	＊
補正Ca（mg/dL）	＜11.0	＜11.0	＊	＊
リンパ節腫大（組織学的に証明済）	No	＊	＋	＊
腫瘍部位				
皮膚	＊＊	＊	＊	＊
肺	＊＊	＊	＊	＊
リンパ節	No	＊	Yes	＊
肝	No	＊	＊	＊
脾	No	＊	＊	＊
中枢神経	No	No	＊	＊
骨	No	No	＊	＊
腹水	No	No	＊	＊
胸水	No	No	＊	＊
消化管	No	No	＊	＊

N ：正常上限
＊ ：条件の制約なし。
＊＊：他の項目が満たされれば不可欠ではない。しかし末梢血の異常リンパ球が5％以下の場合は組織学的に証明された腫瘍病変を必要とする。
a ：末梢血の異常リンパ球が5％以下の場合は組織学的に証明された腫瘍病変を必要とする。

（Br J Haematol. 1991；79：428－437）

14療法である。それ以外にも中小規模の臨床試験が行われたいくつかの治療レジメンがある。

- JCOG9801試験の結果から，VCAP－AMP－VECP療法が本邦でのaggressive ATLに対する標準治療とみなされている[4]（表2）。しかしながら，週1回の治療レジメンであり，また骨髄抑制が強いためにgranulocyte colony stimulating factor（G-CSF）製剤を要する場合が多く，自宅から治療を行う医療機関へのアクセスが悪い場合や高齢者には導入しにくい。そのような場合にはCHOP療法が行われる場合が多い。JCOG9801試験ではCHOP14療法が採用されたが，現在の実臨床としてはCHOP21療法が使用される場合も多い。
  - JCOG9303試験（VCAP－AMP－VECP療法の第Ⅱ相試験）での生存期間中央値は13.0ヵ月であった[5]。
  - JCOG9801試験（VCAP－AMP－VECP療法とCHOP14療法の第Ⅲ相比較試験）での生存期間中央値はVCAP－AMP－

表2 VCAP−AMP−VECP療法のレジメン

	薬剤	投与量	投与日
VCAP	ビンクリスチン	1 mg/m² (maximum 2 mg)	1
	シクロホスファミド	350mg/m²	1
	ドキソルビシン	40mg/m²	1
	プレドニゾロン	40mg/m²	1
AMP	ドキソルビシン	30mg/m²	8
	ラニムスチン	60mg/m²	8
	プレドニゾロン	40mg/m²	8
VECP	ビンデシン	2.4mg/m²	15
	エトポシド	100mg/m²	15, 16, 17
	カルボプラチン	250mg/m²	15
	プレドニゾロン	40mg/m²	15, 16, 17

28日サイクルで6サイクル施行する。
2, 4, 6サイクル開始時に，メトトレキサート15mg，シタラビン40mg，プレドニゾロン10mgの髄腔内投与を行う。

VECP療法群，CHOP14療法群でそれぞれ12.7，10.9ヵ月，3年全生存割合とCR割合はVCAP−AMP−VECP療法とCHOP14療法でそれぞれ23.6%と12.7%，40%と21%であったことから，VCAP−AMP−VECP療法が標準治療と位置づけられた[4]。

- その他，以下のようなレジメンが使用されている。

①ATL−GCSF（VCR+DXR+CPA+PSL+ETP−VDS+MCNU+ミトキサントロン(MIT)）療法[6]

②mEPOCH（ETP+PSL+VCR+CPA+DXR）療法[7]

③OPEC/MPEC（VCR+MTX+ETP+CPA+PSL）療法[8]

④ETP単剤[8]；高齢者など多剤併用化学療法不耐で，比較的緩慢な経過の場合に使用される場合が多い。

Aggressive ATLに対する二次治療は何か？

- 二次治療以降の標準的な治療レジメンは確定していない。ATLでは一次治療で寛解に入ったとしても再発・再燃までの期間が短い場合が多く，ATL以外の悪性リンパ腫に対して行われる治療レジメンでそれまでの治療で使用されていない薬剤を含むものを順次選ぶことになる。
- 2012年5月から抗CCR4抗体モガムリズマブが使用可能となった。CCR4はほとんど全てのATL細胞に発現する膜貫通型蛋白であり，再発・難治性ATLに対する単剤での開発治験では約半数の患者に有効であった[9,10]。今後，実臨床で使用された多数例での有用性評価が待たれる。
- 緩和的な化学療法として，ETP単剤やソブゾキサン単剤が使用される場合がある。

Aggressive ATLに対する造血幹細胞移植の位置づけは？

- 自家移植は早期再発が多く，その有効性は否定されている[11]。
- 同種移植により，30〜40%の患者に長期生存が得られる。これは同種移植を受けなかった集団の長期生存が約10%であること

に比べると良好である[12,13]。この比較は同種移植を受けた患者は初期治療後に一定の全身状態，臓器機能を維持していた集団であることを加味して考慮しなければならないが，日常臨床においては積極的に同種移植を考慮する。

- HTLV-1キャリアの高齢化に伴い，ATLの発症年齢の中央値は67歳となっている。そのため，一般に60歳までとされる骨髄破壊的造血幹細胞移植の適応から外れる患者が多い。厚生労働科学研究費「成人T細胞白血病（ATL）に対する同種幹細胞移植療法の開発とそのHTLV-1排除機構の解明に関する研究」（研究代表者；鵜池直邦）では，ATL患者に対する骨髄非破壊的造血幹細胞移植を血縁，非血縁ドナーで行う第Ⅰ相，第Ⅱ相試験を行い，骨髄破壊的造血幹細胞移植と比べ遜色のない治療成績をあげている[14]。

海外でのaggressive ATLに対する治療は？

- 海外ではインターフェロンα/ジドブジン（IFN/AZT）療法が，急性型に対する標準治療とみなされている。これは，IFN/AZT療法と化学療法を比較した海外での後ろ向き調査で，急性型にはIFN/AZT療法が化学療法より優れ，リンパ腫型では化学療法がIFN/AZT療法より優れるとされているためである[15]。
- Aggressive ATLに対するIFN/AZT療法の海外からの報告は，いずれも症例数が少なく，研究の質が高いとは言えない。
- 海外の報告では，急性型にはIFN/AZT療法が化学療法より優れるとされるが，海外の化学療法による急性型の治療成績はJCOG臨床試験などでの日本のそれと比較し，非常に悪い[15]。日本での急性型に対する化学療法での治療成績を，海外での急性型に対するIFN/AZT療法の成績と単純に比較した場合，勝ることはあっても劣ることはない。したがって，aggressive ATLに対して，本邦がIFN/AZT療法を追従する必要はないと考えられる[16,17]。

Indolent ATLに対する治療は？

- 本邦では急性転化してaggressive ATLになるまで無治療経過観察が行われている。
- 九州・沖縄の約40施設の共同研究として行われた後ろ向き研究で，慢性型の無治療群90例は抗がん剤投与群49例よりも有意に生存期間が長かったという報告がある。慢性型に対して化学療法を行っても予後は改善しないことを示していると考えられるが，化学療法を受けた患者群には臨床的に化学療法が必要と判断される病態が存在していたという背景の違いがあった可能性も否定できない[18]。
- 皮膚病変に対しては，低悪性度皮膚T細胞リンパ腫である菌状息肉症と同様に，症状緩和を目的とした治療が実施される場合があるが，全生存期間延長効果はないとされる[19]。
  - ・皮膚病変に対する局所治療；外用副腎皮質ホルモン，外用抗がん剤，外用レチノイド，光化学療法，外科的切除，局所放射線照射
  - ・皮膚病変に対する全身治療；副腎皮質ホルモン，抗がん剤（少量ETPなど），レチノイド
- 長崎大学から報告されたくすぶり型，慢性型ATLの長期予後の後ろ向き研究では，急性型への移行など増悪するまで無治療経過観察が行われたくすぶり型，慢性型ATL90例（くすぶり型25例，予後不良因子を有する慢性型37例，予後不良因子を有さない

慢性型26例，不明2例）の中で，観察期間中央値4.1年時点で12人が10年以上生存していた。くすぶり型，慢性型間で生存期間中央値に有意差はなく，2年，5年，10年，15年の生存割合はそれぞれ60%，47%，23%，13%，生存期間と無増悪生存期間の中央値はそれぞれ4.1年と3.3年であった。したがって，くすぶり型，慢性型ATLは従来考えられていたように決して「予後良好」ではないことが明らかになってきた[20]。

海外でのindolent ATLに対する治療は？

- 2010年にフランスグループからIFN/AZT療法の後ろ向き症例調査の結果が報告された。初回治療にIFN/AZT療法を受けた慢性型，くすぶり型ATL17例では5年生存割合が100%（観察期間中央値5年）であったのに対し，初回治療に化学療法を受けた慢性型，くすぶり型ATL6例の5年生存割合は42%であった[15]。
- この報告は患者数が極めて少ないこと，慢性型，くすぶり型ATLに対する本邦での標準治療である無治療経過観察の成績が解析に加えられていないこと，さらにIFN/AZT療法を行うか，化学療法を行うかが各施設の判断で決定されているため，IFN/AZT療法と化学療法を受けた患者の背景が同一であったかどうかが全く不明であるなどの問題点があり，科学的な妥当性が担保されているとはいえない。しかしながらあえて単純に比較すると，海外でIFN/AZT療法を受けた患者の予後は，前述の長崎大学から報告された慢性型，くすぶり型ATL患者の予後よりはるかに良好である[20]。
- Indolent ATL患者での有害事象の発生頻度と重篤度，治療コンプライアンス，有効性を正しく評価し，indolent ATL患者にとってIFN/AZT療法が標準治療となりうるのかどうかを検討する必要がある。

ATLの治療成績向上のためには？

- 可能な限り臨床試験に登録し，より優れた治療法の開発を推進する。
- 以下に代表的な臨床試験を挙げる。

①**JCOG0907試験**：「成人T細胞白血病・リンパ腫に対する骨髄破壊的前処置法を用いた同種造血幹細胞移植療法を組み込んだ治療に関する第Ⅱ相試験」（研究責任者；長崎大学　塚崎邦弘，研究事務局；琉球大学　福島卓也）

・aggressive ATL患者の導入化学療法中に血縁・非血縁の骨髄ドナーを検索し，ドナーが得られ移植が可能になった場合は速やかに移植を行い，骨髄破壊的移植を積極的に施行する治療の有用性を明らかにする。本試験の早期の完遂が待たれる。

②**JCOG1111試験**：「成人T細胞白血病・リンパ腫に対するインターフェロンα/ジドブジン併用療法とWatchful waiting療法のランダム化比較試験」（研究責任者；長崎大学　塚崎邦弘，研究事務局；福岡大学　石塚賢治，琉球大学　福島卓也）

・Indolent ATL患者を2群にランダマイズし，IFN/AZT療法が現在の標準治療である無治療経過観察に勝るかどうかを高度医療評価制度下で実施する比較試験。2012年秋には開始できる見込みである。先進国の中で唯一濃厚なHTLV-1 endemic areaをもつ本邦でしか実施できない，indolent ATL診療のランドマークとなりうる試験である。

③**ATL-NST-5試験**：「成人T細胞白血病リンパ腫（ATL）に対する骨髄非破壊的移植前処置を用いた非血縁臍帯血移植の安

全性検討試験」（研究責任者；九州がんセンター　鵜池直邦，研究事務局；九州がんセンター　崔日承）

・急性型あるいはリンパ腫型のATL患者に対して，骨髄非破壊的移植前処置を用いた非血縁臍帯血移植の安全性を検討する試験。

④モガムリズマブの初発aggressive ATLに対する有効性（終了）

・VCAP—AMP—VECP療法にモガムリズマブ併用の有無による比較を行う第Ⅱ相試験，解析結果の報告が待たれる。

⑤その他の臨床試験中あるいは準備中の薬剤

・レナリドマイド
・ボルテゾミブ（医師主導治験）
・プララトレキセート
・デニリューキン・ジフチチオックス

日和見感染症対策[16]

- ATL患者では，細胞性免疫低下による日和見感染（ニューモシスティス・ジロベティ肺炎，カンジダ症，サイトメガロウイルス感染症，糞線虫症など）を起こしやすい。
- ニューモシスティス・ジロベティ肺炎は，致命的な経過をたどることが多く，ATL患者に化学療法を施行する際には，スルファメトキサゾール・トリメトプリム合剤の予防投与を行う。

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Lecture

解　説

成人T細胞白血病・リンパ腫に対するインターフェロンα・ジドブジン併用療法*

石　塚　賢　治**

Key Words : adult T-cell leukemia-lymphoma (ATL), interferon, zidovudine

はじめに

成人T細胞白血病/リンパ腫(ATL)は，human T-lymphotropic virus type-I(HTLV-1)によってひき起こされる末梢性T細胞腫瘍である．現在，日本には110万人程度のHTLV-1キャリアーが存在する．ATL発症は40歳ぐらいから徐々に増加し，60歳後半をピークにして減少する．1人のHTLV-1キャリアーが，生涯でATLを発症する割合は約3～5％程度と考えられている[1)2)]．

1991年に全国実態調査で集められた854例のATL患者のデータから，予後因子として年齢，performance status(PS)，総病変数，高Ca血症，高LDH血症が同定された[3)]．さらに，この予後因子解析と臨床病態の特徴から，くすぶり型，慢性型，リンパ腫型，急性型の4つの病型分類が決定された[4)]．この病型分類は現在も世界的にも広く使用され，ATLに対する治療方針決定に重要な役割を果たしている．慢性型については，BUN＞施設基準値上限，LDH＞施設基準値上限，アルブミン＜施設基準値下限の3つが予後不良因子として同定され，これら予後不良因子のいずれかを有する慢性型の予後は急性型・リンパ腫型と同様に不良であるため「予後不良因子を有する慢性型」，それ以外の慢性型を「予後不良因子を有さない慢性型」と分類している[5)]．さらに最近われわれは，全国81の血液内科医療機関との共同研究で行った後ろ向き調査で2000年から2009年に診断された急性型・リンパ腫型ATL 807例を解析し，病期，PS，年齢，血清アルブミン，血清可溶性インターロイキン2受容体の5つの予後因子を抽出し，ATL-prognostic indexを開発した[6)]．

本邦では，急性型・リンパ腫型と予後不良因子を有する慢性型ATL(aggressive ATL)は強力な多剤併用化学療法が標準治療であり，近年は若年者を中心とする適応例に対しては同種造血幹細胞移植が積極的に取り入れられている．支持療法の進歩もあって，aggressive ATLの治療成績には一定の向上がみられている．しかしながら，くすぶり型と予後不良因子を有さない慢性型(indolent ATL)に対しては，時間経過とともにaggressive ATLに移行していく(急性転化)にもかかわらず，従来からの無治療経過観察が行われているのが現状である．日米欧のATL研究者によって提唱されたATLの治療戦略についての指針を表1に示す[7)]．本稿では，海外では標準治療とみなされながら日本ではまったく行われていないATLの治療オプション，インターフェロンα/ジドブジン併用(IFN/AZT)療法[8)]について概説する．

Aggressive ATLに対するIFN/AZT療法

1995年に米国とフランスのグループがaggressive ATLに対するインターフェロン・ジドブジン併用(IFN/AZT)療法の有効性をそれぞれ報告した[9)10)]．その後，少数例での臨床試験の報告や症例報告

* Combination of interferon α and zidovudine : an option for the treatment of ATL.

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表1　ATLの治療戦略についてのコンセンサスレポートによる治療指針

くすぶり型あるいは予後不良因子を有さない慢性型ATL
- 臨床試験への参加
- 有症候の場合(皮膚病変，日和見感染症など)；IFN/AZT療法あるいはwatch and wait
- 無症候の場合；watch and wait

予後不良因子を有する慢性型あるいは急性型ATL
- 臨床試験への参加
- 化学療法(VCAP-AMP-VECP療法など)±同種造血幹細胞移植
- IFN/AZT療法

リンパ腫型ATL
- 臨床試験への参加
- 化学療法(VCAP-AMP-VECP療法など)±同種造血幹細胞移植

(文献[7]より引用，一部改変)

が行われ(表2)，海外では急性型ATLに対してはIFN/AZT療法が化学療法とともに汎用される治療としてコンセンサスが形成されている(表1)．しかしながら，前向き臨床試験として実施された症例数はきわめて少ない．

2010年にフランスグループからIFN/AZT療法の後ろ向き症例調査の結果が報告された[11]．彼らは1995年から2008年にフランス本国(67例)，米国(59例)，英国(13例)，Martinique(西インド諸島東部のフランス海外県；111例)で診療された合計254例の臨床データを解析している．その結果，IFN/AZT療法はリンパ腫型以外の全病型に対して非常に有効であると結論づけられた(表3)．

本治療法はaggressive ATLのうち，急性型に対して高い有効性を持つ可能性があるものの，“標準治療”と決定するだけの質の高い前向き臨床試験に裏打ちされたエビデンスはなく，適切に計画された前向き試験で有効性を検証する必要がある[7]．Aggressive ATLに対するIFN/AZT療法の治療成績を日本臨床腫瘍研究グループ(JCOG)9303・JCOG9801試験で確立された本邦でのaggressive ATLに対する標準治療であるVCAP-AMP-VECP(ビンクリスチン＋シクロホスファミド＋ドキソルビシン＋プレドニゾロン－ドキソルビシン＋ラニムスチン＋プレドニゾロン－フィルデシン＋エトポシド＋カルボプラチン＋プレドニゾロン)療法と単純に比較すると，奏効率はほぼ同等でMSTはVCAP-AMP-VECP療法のほうが優れるか少なくとも同等と考えられる(表3)[12][13]．有害事象は本邦で実施されている多剤併用化学療法と比較すると，IFN/AZT療法のほうが軽度だが，IFN/AZT療法では有効性がみられるまで30～60日間を要し，治療開始後初期には病勢の進行がみられる場合もある．これらの状況を勘案すると高Ca血症などで急速に病状が悪化することが多いaggressive ATLの初回治療にIFN/AZT療法を導入する魅力は高くはない．また，高薬価のインターフェロン製剤を寛解導入後も長期間継続する必要があるため，医療コストが通常の化学療法よりも高くなることも考えられる．

英国のグループは，CHOP療法を主体とする化学療法にIFN/AZT療法を併用する有効性を後ろ向き調査で報告している．急性型・リンパ腫型とも化学療法単独群よりも，化学療法にIFN/AZT療法を併用したほうが生存期間は有意に延長していた[14]．しかしながらこの報告を解釈する際にも，症例数が少ないことと化学療法群の成績が本邦の臨床試験と比較すると非常に悪いことに

表2　ATLに対するIFN/AZT療法の代表的な報告のまとめ

	Gill et al.[9]	Hermine et al.[20]	Matutes et al.[21]	White et al.[22]	Ramos et al.[23]
[初回治療例]					
CR/PR(%)	CR+PR 58	59/34	0/100	33/33	n.a.
MST(M)	n.a.	11	n.a.	n.a.	n.a.
Subtype of ATL*	n.a.	11/2/0/0	2/1/0/0	3/0/0/0	n.a.
[全例]					
CR/PR(%)	26/32	53/24	0/67	6/11	23/18
MST(M)	3	11	18	6	n.a.
Subtype of ATL*	17/2/0/0	15/4/0/0	13/2/0/0	11/5/2/0	15/4/3/0

CR：complete remission，PR：partial remission，MST：median survival time，M：months，n.a.：not available，
* acute/lymphoma/chronic/smouldering

表3 ATLに対する治療成績：本邦と海外の比較

[フランスグループの統合解析[11]]

First line treatment	Acute		Lymphoma		Chronic and smouldering	
	IFNα/AZT (n=45)	Chemotherapy (n=53)	IFNα/AZT (n=13)	Chemotherapy (n=47)	IFNα/AZT (n=17)	Chemotherapy (n=6)
MST	9M	6M	7M	16M	not reached	60M
5-year OS	28%	10%	0 %	18%	100%	42%

[本邦の臨床試験と後ろ向き調査[12)13)16)]]

First line treatment	Acute		Lymphoma		Chronic and smouldering
	Chemotherapy		Chemotherapy		Watch and waiting (n=90)
	JCOG9303 (n=56)	JCOG9801 (n=39)	JCOG9303 (n=27)	JCOG9801 (n=12)	
MST	11M	13M	20M	14M	49M
3-year OS	n.a.	23%	n.a.	17%	47%(5-years)

は注意を要する．

Indolent ATLは「予後良好」な疾患か？

くすぶり型，慢性型ATLは「予後良好」な疾患と考えられてきた．病型分類が決定された1991年の解析(観察期間中央値13.3か月)では，生存期間中央値は慢性型で24.3か月，くすぶり型は未到達であった[4]．急性型の6.2か月，リンパ腫型の10.2か月に比べれば確かに予後は良好であった．

くすぶり型，慢性型ATLから「予後不良因子を有する慢性型」を除いたindolent ATLに対する日本の治療戦略は，急性転化してaggressive ATLになるまで無治療経過観察を行うことである．しかし，この治療方針も質の高いエビデンスに裏づけられたものではない．九州・沖縄の約40施設の共同研究として行われた後ろ向き研究で，慢性型の無治療群90例は抗がん剤投与群49例よりも有意に生存期間が長かった(生存期間中央値：7.4年 vs. 2.0年)という報告がある．慢性型に対して化学療法を行っても予後は改善しないことを示していると考えられるが，化学療法を受けた患者群には臨床的に化学療法が必要と判断される病態が存在していたという背景の違いがあった可能性も否定できないことも同時に指摘されている[15]．

昨年，長崎大学からくすぶり型，慢性型ATLの長期予後の後ろ向き研究が報告された．急性型への移行など増悪するまで無治療経過観察が行われたくすぶり型，慢性型ATL 90例(くすぶり型25例，予後不良因子を有する慢性型37例，予後不良因子を有さない慢性型26例，不明2例)の中で，観察期間中央値4.1年時点でくすぶり型，慢性型間で生存期間中央値に有意差はなく，2年，5年，10年，15年の生存割合はそれぞれ60%，47%，23%，13%，生存期間と無増悪生存期間の中央値はそれぞれ4.1年と3.3年であった[16]．われわれが行った全国調査でも，くすぶり型，慢性型ATLの長期予後は，長崎大学からの報告とほぼ同様であった(未公表)．

これらの情報から得られることは，くすぶり型，慢性型ATLは決して「予後良好」ではないことである．生存期間中央値が5年に満たない患者群を「予後良好」として無治療経過観察することは妥当であろうか．われわれは，イマチニブが導入されるまで慢性骨髄性白血病慢性期の患者に対し，発熱や強い倦怠感があっても患者を説得しながらインターフェロン製剤を投与し，さらには20%程度の治療関連死を犠牲にしながら同種造血幹細胞移植を行ってきた．くすぶり型，慢性型ATLの5年生存割合50%程度というのは，イマチニブ導入前の慢性骨髄性白血病慢性期の患者の予後とほぼ同じであることもまた事実である．

Indolent ATLに対するインターフェロン・ジドブジン併用療法の現状

前述のフランスグループのIFN/AZT療法の後ろ向き症例調査によると，初回治療にIFN/AZT

療法を受けた慢性型，くすぶり型ATL 17例では5年生存割合が100％であったのに対し，初回治療に化学療法を受けた慢性型，くすぶり型ATL 6例のそれは42％であった．この報告は患者数がきわめて少ないこと，慢性型，くすぶり型ATLに対する本邦での標準治療である無治療経過観察の成績が解析に加えられていないこと，さらにIFN/AZT療法を行うか，化学療法を行うかが各施設の判断で決定されているため，IFN/AZT療法と化学療法を受けた患者背景が同一であったかどうかがまったく不明であるといった問題点があり，科学的な妥当性が保証されてはいない．しかしながらあえて単純に比較すると，海外でIFN/AZT療法を受けた患者の予後は，本邦の慢性型，くすぶり型ATL患者の予後よりはるかに良好である(表3)．

ATLの予後向上に向けてindolent ATLの治療開発をどう行うか

Aggressive ATLに対してはATL細胞に特異的に発現するCCR4抗原を標的とした抗体療法が2012年5月に導入されたほか，いくつかの新規薬剤の導入が期待される．

Indolent ATLに治療介入を行う目的は，末梢血ATL細胞の減少，リンパ節の縮小，血清LDH低下というような短期的な抗腫瘍効果を得ることではない．急性転化するまでの期間と全生存期間の延長が得られることが必要である．皮膚に病変の主座のあるくすぶり型ATLに対する外用や内服の副腎皮質ホルモン剤，あるいは放射線治療や光化学療法などの局所治療は症状緩和には有効であるが，生存期間の延長は明らかではない[17]．治療強度の弱い化学療法剤や副腎皮質ホルモン剤はindolent ATLに対しても抗腫瘍効果は示すが，細胞性免疫低下状態を伴うATL患者にこれらの薬剤を使用することは易感染状態をさらに惹起する．また，治療によって腫瘍細胞が化学療法剤に対して耐性を獲得し，急性転化後の治療選択肢を失ったり，化学療法剤に耐性を獲得したのでは意味がない．したがって，急性転化の防止あるいは急性転化までの期間の延長によって，全生存期間が延長しない限りは，indolent ATLに対する治療介入は意味がない．

2001年に報告された第9次ATL全国実態調査当時では発症年齢平均値61歳であったが，主に出生コホートによるHTLV-1キャリアー数の自然減によってキャリアーが高齢化しているため，2010年に報告された発症年齢中央値は67歳となっており，患者層の高齢化が進んでいる．今後はATL患者の発生は緩徐に減少していくであろうが，新規ATL患者はしだいに高齢化していく．高齢者aggressive ATLに対しては，強力な治療が行えない場合も多いことを考慮すると，特に高齢のindolent ATL患者に対しては有効な治療介入を行い，急性転化するまでの期間を延長できれば理想的である．

Indolent ATL患者に治療介入を行う場合には，有効性と有害事象のバランス，さらにはコストも考慮に入れることが重要である．多くのindolent ATL患者は急性転化に対する不安は感じていても，全身状態の悪化を自覚していることは少ないので，「差し迫った」生命の危機は感じていない．そのような患者群を対象にする治療介入においては，許容される有害事象はそれによって得られるメリットの大きさによって決定される．治療コストも同様である．

今後，indolent ATLからaggressive ATLに移行する高危険群を抽出できたならば，それらの高危険群indolent ATL患者を対象に治療介入を行うことによって，集団としての治療効率を高めて治療の有害事象によるデメリットを相殺することが可能となる．くすぶり型ATLでの皮膚病変の存在はaggressive ATLに移行する高危険群である可能性が指摘されてきたが[18)19)]，現在進行中のHTLV-1感染者コホート研究(JSPFAD)の前向き研究で蓄積される情報等を生かして，分子生物学的な手段を駆使したより詳細な解明が期待される．

おわりに

海外の後ろ向き研究で報告されたIFN/AZT療法の驚異的ともいえる有効性は，いくつかの疑問点があり懐疑的にならざるを得ないものの，再現性をもって証明されたならば非常に魅力的な治療法である．急性型・リンパ腫型ATLに対するIFN/AZT療法の既報によると，好中球減少，