alone (n = 33), (2) cyclosporine + short-term methotrexate (MTX) (n = 45), and (3) cyclosporine + mycophenolate mofetil (MMF; n = 12). Tacrolimus-based prophylaxis was subdivided into 4 groups as follows: (1) tacrolimus alone (n = 37), (2) tacrolimus + short-term MTX (n = 32), (3) tacrolimus + MMF (n = 5), (4) and tacrolimus + prednisolone (n = 3). Ninety-four patients (54%) received CBT < 200 days after diagnosis. One hundred twenty-four (71%) patients underwent CBT with 2 HLA-mismatched loci. The numbers of infused nucleated and CD34-positive cells were 2.58×10^7/kg (range, .36 to 5.34×10^7/kg) and $.85 \times 10^5$/kg (range, .07 to 5.39×10^5/kg), respectively. Engraftment evaluation was possible in 125 patients (71%) within a median interval of 19 days after CBT (range, 7 to 46 days). Among the survivors, the median follow-up duration was 22.5 months (range, 0 to 74.5 months).

Prognostic Factors for Survival

The OS rates of 175 patients with ATLL who received CBT were 30.2% (95% confidence interval [CI], 23.0% to 37.4%) at 1 year and 20.6% (95% CI, 13.8% to 27.4%) at 2 years (Figure 1A). The cumulative incidence rates of ATLL-related mortality and TRM at 2 years were 31.9% (95% CI, 24.8% to 39.3%) and 46.4% (95% CI, 38.5% to 54.0%), respectively (Figure 1B). The following confounding factors affected survival: age, gender, disease status at transplantation, days from diagnosis to transplantation, date of transplantation, age at transplantation, conditioning regimen, number of infused nucleated and CD34-positive cells, ABO compatibility, HLA compatibility, GVHD prophylaxis, and the development of acute GVHD. A univariate analysis revealed that higher OS ($P < .05$) correlated with CR at transplantation, minor ABO incompatibility, the addition of other agents to calcineurin inhibitors (MTX or MMF), and the development of acute GVHD (Table 2). A multivariate analysis was performed to further examine the effects of an age <55 years, the development of acute GVHD as a time-dependent covariate coincident with CR at transplantation, minor ABO incompatibility, and the addition of other agents to calcineurin inhibitors (Table 3). Compared with the absence of GVHD, the development of acute GVHD was associated independently with higher OS (hazard ratio [HR], .10; 95% CI, .01 to 0.94; $P = .044$).

Effects of Acute GVHD on Survival

To further validate the effect of acute GVHD on OS, we examined survival according to the acute GVHD grade in a landmark analysis. The median time to onset of acute GVHD of any grade after transplantation was 21 days (range, 5 to 100 days). Acute GVHD occurred in 80 patients (46%) as

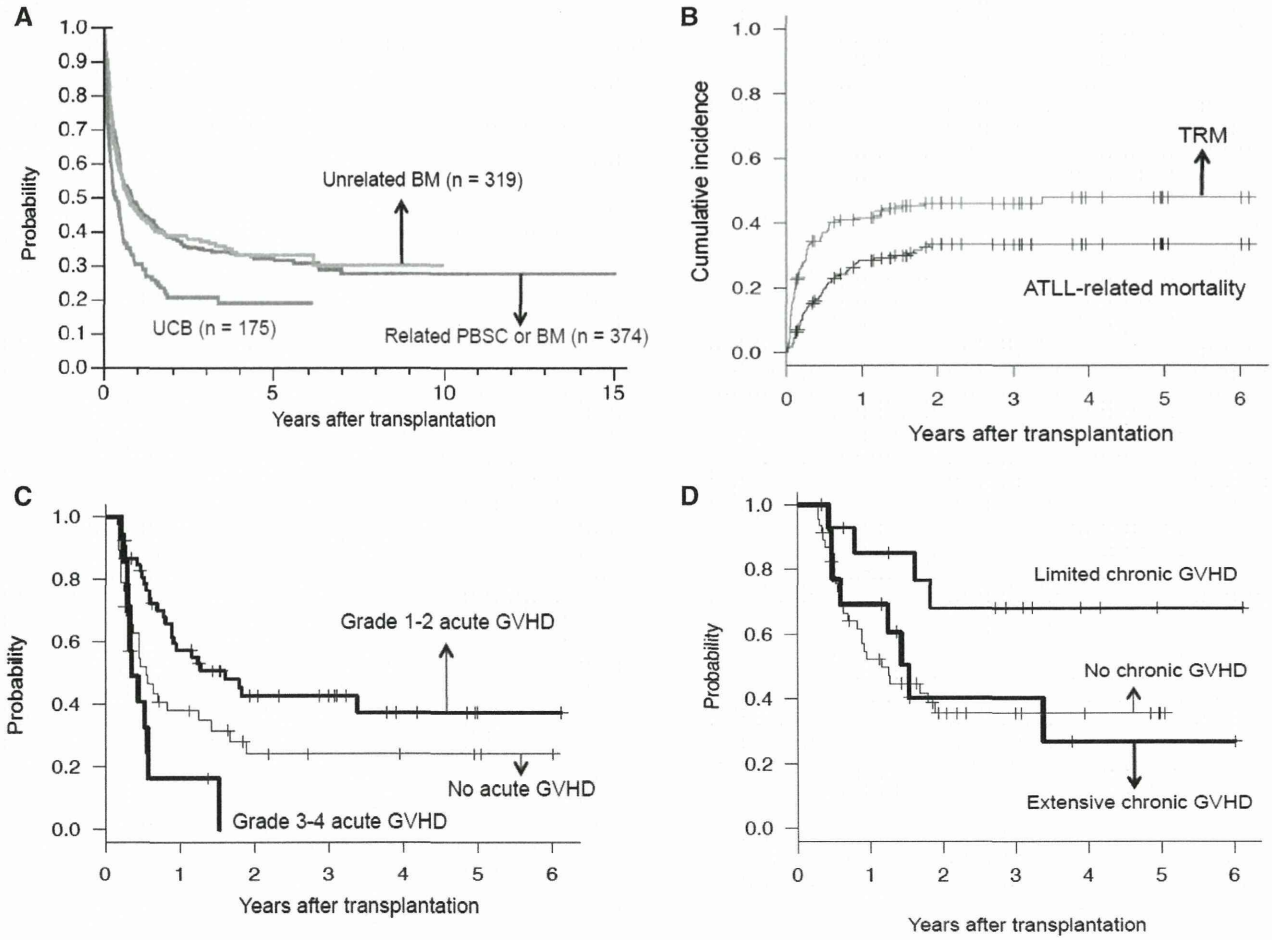

Figure 1. Survival, adult T cell leukemia/lymphoma (ATLL)-related mortality rates, and transplantation-related mortality (TRM) rates of patients receiving cord blood transplantation (CBT). (A) Kaplan-Meier curves of the estimated overall survival rates (OS) of ATLL patients treated with CBT. UCB, umbilical cord blood; PBSC, peripheral blood stem cells; BM, bone marrow, GVHD, graft-versus-host disease. (B) Cumulative incidence curves of ATLL-related mortality and TRM in patients treated with CBT. (C) Landmark plots of OS to determine the effects of acute GVHD. (D) Landmark plots of OS to determine the effects of chronic GVHD.

Table 2
Univariate Analysis of Risk Factors for Overall Survival

Variables		No.	OS		
			Two-Year OS (%)	95% CI	*P* Value
Age 1	<60 yr	134	23.0	15.0-31.0	.080
	≥60 yr	41	12.0	6.0-22.4	
Age 2	<55 yr	85	25.4	15.0-35.8	.100
	≥55 yr	90	15.6	7.0-24.2	
Sex	Female	70	22.3	11.5-33.1	.453
	Male	105	19.4	10.8-28.0	
Disease status at transplantation	CR	50	40.3	25.5-55.1	.003
	Not in CR	116	14.3	7.1-21.7	
Time from diagnosis to transplantation	<200 d	94	22.4	12.8-32.0	.752
	≥200 d	75	19.9	9.7-30.1	
Yr of transplantation	<2005	71	17.6	8.2-27.0	.160
	≥2005	104	23.1	13.5-31.5	
Conditioning regimen	FIC	63	20.2	9.8-30.6	.740
	RIC	108	20.2	11.8-28.6	
Infused nucleated cell dose ($\times 10^7$/kg)	<2	19	10.8	0-29.3	.290
	≥2	145	22.6	14.9-30.3	
Infused CD34 cell dose ($\times 10^5$/kg)	<1	97	23.3	13.9-32.7	.396
	≥1	66	19.1	8.0-30.2	
ABO matching	Matched	56	12.8	3.4-22.2	.024
	Minor mismatched	49	30.5	15.5-45.5	
	Major mismatched	69	20.5	9.9-31.1	
HLA matching	0 mismatched	5	30.0	0-77.4	.525
	1 mismatched	36	21.6	5.6-37.6	
	2 mismatched	73	24.6	14.3-35.9	
	≥3 mismatched	42	18.1	3.9-32.3	
GVHD prophylaxis 1	Cyclosporine-based	90	21.9	12.5-31.4	.710
	Tacrolimus-based	77	20.3	10.0-30.4	
GVHD prophylaxis 2 (cyclosporine/tacrolimus + other drug)	No	70	12.4	4.8-20.0	.003
	Yes	97	32.7	21.1-44.3	
Acute GVHD	No	59	16.8	5.7-27.9	<.0001
	Yes	80	29.4	18.2-40.6	

follows: grade 1, n = 23 patients; grade 2, n = 37 patients; grade 3, n = 14 patients; and grade 4, n = 6 patients. There was no significant difference in OS between patients with grades 1 and 2 GVHD ($P = 1.00$), in contrast to the difference between patients with grades 1 and 3 GVHD ($P = .013$). Moreover, based on the previous national survey analysis of the effect of acute GVHD on survival in patients with ATLL [5,15], the effect of acute GVHD on OS in the present study was evaluated using landmark plots (landmark day 60) according to the following 3 categories: (1) no acute GVHD (n = 38), (2) grade 1 to 2 acute GVHD (n = 53), and (3) grade 3 to 4 acute GVHD (n = 14). The 2-year OS rates for patients according to the acute GVHD grade were as follows: 24.2% (95% CI, 11.2% to 39.8%) without acute GVHD; 42.7% (95% CI, 28.1% to 56.6%) with grade 1 to 2 GVHD; and 0% with grade 3 to 4 GVHD (Figure 1C). These analyses demonstrated that the development of grade 1 to 2 acute GVHD was associated with higher OS compared with the absence of acute GVHD ($P = .048$), whereas the development of grade 3 to 4 acute GVHD was associated with lower OS compared with that in patients with grade 1 to 2 acute GVHD ($P = .0003$). The cumulative 2-year ATLL-related mortality rates according to the GVHD grades were as follows: 32.6% (95% CI, 19.7% to 46.1%) for grade 1 to 2 acute GVHD; 29.8% (95% CI, 8.2% to 55.6%) for grade 3 to 4 acute GVHD; and 45.9% (95% CI, 29.0% to 61.3%) for no acute GVHD. There was a trend toward a lower risk of relapse or progression in those who developed grade 1 to 2 acute GVHD relative to those without GVHD. Among patients with non-CR at transplantation, there was also a trend toward higher 2-year OS (36.7%; 95% CI, 18.7% to 54.9%) in those who developed grade 1 to 2 acute GVHD than in those without GVHD (15.6%; 95% CI, 3.4% to 35.9%). These data suggested a graft-versus-ATLL effect induced by CBT.

Table 3
Multivariate Analysis of Risk Factors for OS

Variables	OS		
	HR	95% CI	*P* Value
Age, yr			
<55	1		
≥55	1.15	.63-2.09	.652
Disease status at transplantation			
CR	1		
Not in CR	1.38	.73-2.63	.190
ABO matching			
Matched	1		
Minor mismatched	.56	.25-1.24	.152
Major mismatched	.77	.39-1.48	.337
GVHD prophylaxis (cyclosporine/ tacrolimus + other drug)			
No	1		
Yes	.76	.42-1.38	.365
Acute GVHD (time-dependent covariate)			
No	1		
Yes	.10	.01-.94	.044

Effects of Chronic GVHD on Survival

Chronic GVHD was evaluated in 74 patients who survived for at least 100 days after transplantation. Chronic GVHD occurred in 28 patients (37%) with a median time to onset of 115 days (range, 73 to 1287 days) after CBT. The effect of chronic GVHD on OS was evaluated using landmark plots (landmark day 100), and the 2-year OS results were as follows: no chronic GVHD (n = 46), 35.6% (95% CI, 21.0% to 50.0%); limited chronic GVHD (n = 15), 68.1% (95% CI, 35.4%

to 86.8%); and extensive chronic GVHD (n = 13), 40.4% (95% CI, 13.4% to 66.4%) (Figure 1D). There was a trend toward a higher OS among patients with limited chronic GVHD, but there were no significant differences relative to patients without chronic GVHD ($P = .10$) and those with extensive chronic GVHD ($P = .12$).

Cause of Death

At the last follow-up, 46 patients remained alive and 129 were deceased. The median follow-up time among the survivors was 22.5 months (range, 0 to 74.5 months). Disease progression (n = 52) was the leading cause of death. Infection was the cause of death in 40 patients (31%; bacterial, n = 27 patients; fungal, n = 3; viral, n = 8; and others, n = 2). Viral infection-related deaths were caused by the following pathogens: cytomegalovirus, n = 3; adenovirus, n = 2; human herpesvirus-6, n = 2; and varicella-zoster virus, n = 1. Among the 27 patients who succumbed to bacterial infection, 16 died before engraftment at a median of 17 days after CBT (range, 7 to 38 days). Among the 20 patients who developed severe acute grade 3 to 4 GVHD, 2 remain alive without disease progression. However, 9 of the 20 patients died of GVHD, 5 of disease progression, and 4 of infection.

The Fine and Gray proportional hazards model was applied to identify the variables affecting ATLL-related mortality and TRM. The pretransplantation variables included age, gender, disease status at CBT, days from diagnosis to transplantation, age at transplantation, conditioning regimen, number of infused nucleated cells, ABO compatibility, HLA compatibility, and GVHD prophylaxis. The following pretransplantation factors associated with a higher risk of ATLL-related mortality were identified in a multivariate analysis: not in CR at CBT (HR, 3.37; 95% CI, 1.12 to 10.2; $P = .032$) and an age > 55 years at CBT (HR, 2.32; 95% CI, .98 to 5.48; $P = .054$). The following pretransplantation factors were associated with a marginally higher risk of TRM: lower number of infused nucleated cells ($\geq 2 \times 10^7$/kg versus $< 2 \times 10^7$/kg; HR, .56; 95% CI, .30 to 1.02; $P = .059$) and GVHD prophylaxis with a calcineurin inhibitor alone (additional agents plus calcineurin inhibitors versus calcineurin inhibitors alone; HR, .60; 95% CI, .34 to 1.07; $P = .064$).

DISCUSSION

We present here the results of the largest retrospective study of ATLL patients receiving CBT; these results have extended our knowledge relative to that gained from other studies, which were limited by the numbers of cases [15,20,21]. Because graft source selection is strongly influenced by the donor availability, it is difficult to directly compare the outcomes of CBT with those of other allo-HSCT modalities. Nevertheless, the outcome of CBT for ATLL in the previous nationwide survey, with a 3-year OS rate of 17%, was clearly unsatisfactory because the study period corresponded with the developmental phase of CBT in adult patients [15]. Recent improvements in the outcome of CBT have been expected after optimization of the number of cells used for CBT and the improved HLA-compatibility of cord blood units [29-31]. Consequently, a recent nationwide survey data of adults with acute non-ATLL leukemia revealed no differences in the outcome of CBT in comparison with those of other allo-HSCT modalities [18,19]. However, the updated data (through December 2009) indicated that CBT for ATLL remained associated with a poorer 3-year OS of 20.6%, compared with OS of 34.4% among the 374 patients who received related BM or PBSC and 37.1% among the 319 patients who received unrelated BM ($P < .0001$) (Figure 1A). Therefore, the aim of the present study focused on the feasibility of CBT in the context of a larger cohort of patients with ATLL.

In the present study, 2 important findings were identified regarding CBT for ATLL. First, CBT cured patients with ATLL partly through a graft-versus-ATLL effect. Second, the high rate of TRM (approximately 50%) remains a significant problem. The OS curve for ATLL patients who received CBT reached a plateau by 3 years, suggesting long-term survival of selected patients, although the outcome of CBT for ATLL (3-year OS, 20%) did not compare favorably with those of other allo-HSCT modalities. Regarding the prognostic factors affecting survival, our present univariate analysis identified the 5 following significant variables associated with higher OS: (1) age, (2) disease status at transplantation, (3) ABO compatibility, (4) addition of agents such as MTX or MMF to calcineurin inhibitors for GVHD prophylaxis, and (5) development of acute GVHD. Further, the multivariate analysis revealed that the development of acute GVHD was independently associated with better OS relative to the absence of acute GVHD. A landmark analysis showed that the development of grade 1 to 2, or so called mild-to-moderate acute GVHD, was associated with better OS when compared with the absence of acute GVHD. There was also a trend toward a lower risk of relapse or progression with the development of acute GVHD when compared with the absence of GVHD and better OS in patients with limited chronic GVHD. Taken together, these data suggest the presence of a curative graft-versus-ATLL effect conferred by CBT.

However, it is typically difficult for physicians to optimize the effects of acute GVHD to prevent disease progression via graft-versus-ATLL. Therefore, a more realistic attempt would be the control of pretransplantation factors that might affect the CBT outcome and, thus, enhance the benefit of allo-HSCT. The multivariate analysis performed herein with respect to ATLL-related deaths identified disease status at CBT as the most important factor. ATLL usually resists conventional chemotherapy and must be treated soon after diagnosis because of the rapid proliferation of tumor cells, which generates a high tumor burden [2,3]. In the future, novel agents, such as mogamulizumab, a humanized anti-CCR4 monoclonal antibody, might improve CBT-associated survival by decreasing the tumor burden before transplantation [32-35]. Another possibility for improving survival might be reducing the time from diagnosis to transplantation while patients with ATLL remain chemosensitive. Moreover, CBT provides a considerable advantage for patients who require urgent allo-HSCT to combat aggressive ATLL.

In the present study, we have shown that CBT is feasible and curative. However, the high rate of TRM remained a significant problem. Bacterial infection caused the highest incidence of death (21%) during the neutropenic period. The infusion of lower numbers of nucleated cells ($< 2 \times 10^7$/kg), which is usually associated with delayed engraftment, was marginally associated with TRM. Neutrophil recovery is slower in patients treated via CBT, and immunosuppressed patients with ATLL might be at an increased risk of developing more frequent opportunistic infections [36]. Improved supportive care to prevent bacterial infection is required after CBT for patients experiencing a prolonged neutropenic period. The ongoing development of better graft engineering [37] or double-CBT [38] might facilitate rapid neutrophil recovery and, thus, help to reduce the TRM rate in CB recipients.

The present study has several limitations. First, our results concerning the effect of chronic GVHD on survival should be interpreted with caution because the relatively small number of patients who developed chronic GVHD did not allow us to evaluate the effect of this condition on survival in a multivariate analysis. Instead, we were limited to performing a landmark analysis of OS according to the severity of chronic GVHD. Certainly, we detected a trend toward higher OS in patients with limited chronic GVHD when compared with patients without chronic GVHD, suggesting the possible presence of a graft-versus-ATLL effect. However, these results might be biased because of insufficient statistical power. Our future studies will assess the effect of chronic GVHD on the outcome of CBT for the treatment of ATLL after a long-term follow-up. Although the present study employed, to our knowledge, the largest cohort of CBT-treated patients to date and our results demonstrated that CBT is a feasible and effective treatment, this was a retrospective analysis. Therefore, this finding requires confirmation in prospective studies. To establish reliable criteria for CBT administration, a prospective multicenter clinical trial is underway in Japan to evaluate the safety and efficacy of CBT combined with Flu, Mel, and low-dose TBI (4 Gy) along with GVHD prophylaxis (tacrolimus and MMF [39]).

In conclusion, CBT is feasible and effective for patients with ATLL and acts via a graft-versus-ATLL effect. However, the outcome of CBT is unsatisfactory when compared with those of other allo-HSCT modalities. The high rate of TRM must be reduced, and the development of novel strategies is required to further improve the outcome of CBT.

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ORIGINAL ARTICLE

Reduced carotid intima–media thickness in systemic lupus erythematosus patients treated with cyclosporine A

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Abstract

Background Patients with systemic lupus erythematosus (SLE) are at risk of atherosclerosis. An increased carotid intima–media thickness (IMT) is considered to be a marker of early atherosclerosis.

Objective To determine influential factors for increased carotid IMT in SLE patients.

Methods We evaluated the impact of conventional risk factors for atherosclerosis on carotid IMT in 427 healthy controls and of clinical factors on carotid IMT in 94 SLE patients. Carotid IMT was measured by using a newly developed computer-automated system. Unconditional logistic regression was used to assess the adjusted odds ratios (ORs) and 95 % confidence intervals (95 % CI).

Results Multivariate-adjusted mean carotid IMT (mm) was significantly reduced in SLE patients (0.51, 95 % CI = 0.36–0.66) compared to healthy controls (0.55, 95 % CI = 0.40–0.70) ($P = 0.003$). The SLE Disease Activity Index (SLEDAI) was associated with carotid IMT in a dose-dependent manner ($P_{trend} = 0.041$). The current use of cyclosporine A (adjusted OR = 0.02, 95 % CI = 0.01–0.40, $P = 0.011$) and a history of steroid pulse therapy (adjusted OR = 0.01, 95 % CI = 0.01–0.25, $P = 0.006$) were significantly associated with a decreased risk of increased carotid IMT.

Conclusions Our findings suggest that the current use of cyclosporine A can protect against increased carotid IMT, leading to a decreased risk of arteriosclerosis. Future studies with a larger sample size need to confirm that this association holds longitudinally.

Keywords Cyclosporine A · Carotid intima–media thickness · Systemic lupus erythematosus · Risk factor

Introduction

Systemic lupus erythematosus (SLE) exhibits a bimodal pattern of mortality, where early deaths are caused by uncontrolled disease activity, while later deaths are mostly attributed to cardiovascular complications [1]. Subsequent follow-up studies have demonstrated that the incidence of coronary artery disease in women with SLE is five to nine times higher compared with the general population [2–4]. These data indicate that there is a strong association between SLE and cardiovascular diseases. As the main etiological cause of cardiovascular diseases can be attributed to atherosclerosis, the assessment of risk factors for atherosclerosis is important for the control of morbidity and mortality in SLE.

The status of atherosclerosis has been assessed by a number of surrogate markers. The structural markers include such measures as carotid intima–media thickness (IMT) and the presence of plaques, while functional

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markers are for example pulse wave velocity and flow-mediated dilatation of arteries. Among the measures, most of longitudinal studies have demonstrated the usefulness of carotid IMT in predicting future vascular events including myocardial infarction and stroke, which was confirmed by a recent meta-analysis [5]. Carotid IMT evaluated by B-mode ultrasonography has become a simple and non-invasive measure for early atherosclerosis. However, carotid IMT has some difficulties in accuracy and reproducibility, because it is evaluated by the manual eye-measurement method, usually at only three sites each of the carotid arteries. To resolve these problems, a new computer-automated system using Intimascope® software was developed, which enabled the averaging approximately 250 points in 2 cm of carotid artery, therefore being highly useful in carotid IMT measurement [6, 7].

We here compared conventional risk factors for atherosclerosis, including carotid IMT measured by using the newly developed computer-aided system, in a case control study including 92 SLE patients and 184 healthy controls in a female Japanese population. In addition, we evaluated the impact of conventional factors for atherosclerosis on carotid IMT in 427 healthy controls (both sexes) and the impact of clinical status and treatment on carotid IMT in 92 SLE patients.

Patients and methods

Patients and controls

The 92 patients with SLE enrolled in the study were all women and fulfilled the American College of Rheumatology classification criteria for SLE, followed at the Department of Medicine and Biosystemic Science, Kyushu University, from 2007 to 2008. Controls (243 men and 184 women) were recruited from the Human Dry Dock Center, Wellness (Fukuoka, Japan), for a routine health evaluation in September, 2002. Blood samples were obtained from SLE patients and healthy controls in a fasting state. Serum concentrations of total cholesterol (T-chol), triglyceride, HDL cholesterol (HDL-chol), fasting blood sugar (FBS), glycosylated hemoglobin (HbA_{1c}) and high-sensitivity C-reactive protein (CRP) were measured. Serum concentrations of LDL cholesterol (LDL-chol) were calculated by the Friedewald formula [8]. The details of the control group were reported elsewhere [6]. Disease activity was measured by the SLE disease activity index (SLEDAI)[9] and damage by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [10]. Part of the data has been reported previously [6]. All individuals were Japanese. The study protocol was approved by our institutional review board, and all participants provided written informed consent.

Statistical analysis

Comparison of means and proportions between two groups was done by t test and χ^2 test, respectively. Among three groups, P values were calculated by analysis of covariance and were adjusted by use of the Bonferroni correction. The trend of association between clinical status and carotid IMT was assessed by a regression model assigning ordinal scores to the levels of the independent variable. Unconditional logistic regression was used to compute the odds ratios (ORs) and their 95 % confidence intervals (CIs) with adjustments for several covariates. A continuous variable was used for age, and the remaining covariates were treated as a categorical variable. Multicollinearity among all independent variables was evaluated by Pearson correlation. The covariates were basically categorized into three categories using tertiles in the controls as cutoff points. The distribution of CRP concentrations was skewed to the right, and natural logarithms of these values were used in the statistical analysis. The cumulative steroid dose was estimated using the equation 1/2 (maximum steroid dose + current steroid dose) × (the duration of administration). Body mass index (BMI, kg/m^2) was classified into three groups (<19.8, 19.9–21.4 and >21.5); FBS (mg/dl) into three groups (<86, 87–92, >93); carotid IMT (mm) into three groups (<0.50, 0.51–0.57 and >0.58); T-chol (mmol/l) into three groups (<190, 191–217 and >218); DBP (mmHg) into three groups (<57, 58–65 and >66) and CRP (mg/dl) into three groups (<0.016, 0.017–0.045 and >0.046). The estimated steroid dose (g) was categorized into two groups (<127.75 and ≥127.75); SLEDAI into three groups (0–2, 3–5 and ≥6) and SDI into two groups (0–1 and ≥2). When multicollinearity exists, the standard errors for the coefficients tend to be very large, inflating the standard errors of the regression coefficients, which in turn become unreliable. Triglycerides, HDL-chol and LDL-chol were significantly related to and suspected to have multicollinearity with total cholesterol [$r = 0.35$ ($P < 0.001$), $r = 0.12$ ($P = 0.017$) and $r = 0.81$ ($P < 0.001$), respectively] in healthy controls. HbA_{1c} was excluded from the multivariate analysis because of the collinearity between FBS and HbA_{1c} ($r = 0.83$, $P < 0.001$). Similarly, we did not include SBP in multivariate models because of collinearity between DBP and SBP ($r = 0.84$, $P < 0.001$). We also excluded body fat (%) because of collinearity between BMI and body fat ($r = 1.00$, $P < 0.001$). Lastly, disease duration was excluded from the multivariate analysis because of high correlation with age ($r = 0.60$, $P < 0.001$).

All statistical analyses were performed using the computer program STATA version 12.1 (STATA Corp., College Station, TX, USA). All P values were two-sided, with those less than 0.05 considered statistically significant.

Results

Table 1 shows a comparison of the risk factors for atherosclerosis between SLE patients and healthy controls in a female Japanese population. The mean age of SLE patients (43.7, 95 % CI = 41.0–46.4) was not significantly different from that of controls (45.7, 95 % CI = 44.5–47.0; data not shown). Female SLE patients (20.0, 95 % CI = 15.1–25.0) showed significantly lower BMIs than female healthy controls (21.3, 95 % CI = 16.4–26.2; $P = 0.004$). DBP (mmHg) ($P < 0.0001$) was significantly higher in SLE patients (75.5, 95 % CI = 58.4–92.6) than in healthy controls (64.0, 95 % CI = 47.0–80.9), while carotid IMT ($P = 0.003$) was significantly lower in SLE patients (0.51 mm, 95 % CI = 0.36–0.66) compared to healthy controls (0.55 mm, 95 % CI = 0.40–0.70). SLE patients showed marginally lower T-chol ($P = 0.064$) and marginally higher CRP ($P = 0.059$) than healthy controls.

Comparison of selected characteristics between healthy subjects in the highest quartile of carotid IMT (≥0.63 mm) and those in the remaining three quartiles (<0.63 mm) is shown in Table 2. Subjects in the highest quartile showed higher age ($P < 0.001$), prevalence of male sex ($P = 0.002$), and levels of FBS ($P = 0.001$), T-chol ($P = 0.005$), LDL-chol ($P < 0.001$), HbA_{1c} ($P < 0.001$), CRP ($P = 0.001$), BMI ($P < 0.001$), DBP ($P < 0.001$) and SBP ($P < 0.001$) than those in the remaining three quartiles. In contrast, the HDL-chol level was significantly lower in subjects in the highest quartile than in those in the remaining three quartiles ($P = 0.005$).

Detailed characteristics of our SLE patients including the number of each treatment, average and cumulative steroid dose, and disease duration are demonstrated in Table 3. Table 4 shows the association between disease activity or disease damage and carotid IMT in SLE patients. After adjustment for age, FBS, BMI, T-chol, DBP

Table 1 Comparison of risk factors for atherosclerosis between SLE patients and healthy controls in a female Japanese population

	SLE patients ($n = 92$)	Female controls ($n = 184$)	P
BMI (kg/m^2)			
Crude	21.1 (20.5–21.6)	21.1 (20.7–21.5)	0.874
Age-adjusted	21.1 (20.6–21.7)	21.1 (20.7–21.5)	0.876
Multivariate-adjusted[a]	20.0 (15.1–25.0)	21.3 (16.4–26.2)	0.004
T-chol (mmol/l)			
Crude	197 (190–205)	205 (200–210)	0.105
Age-adjusted	199 (193–206)	204 (199–209)	0.267
Multivariate-adjusted[a]	195 (134–257)	206 (144–267)	0.064
FBS (mg/dl)			
Crude	89.8 (85.5–94.0)	91.9 (89.4–94.3)	0.397
Age-adjusted	89.9 (85.7–94.1)	91.7 (89.3–94.1)	0.467
Multivariate-adjusted[a]	88.1 (55.6–121)	92.6 (60.3–125)	0.119
CRP (mg/dl)[b]			
Crude	0.04 (0.03–0.06)	0.02 (0.02–0.03)	0.004
Age-adjusted	0.05 (0.03–0.06)	0.02 (0.02–0.03)	<0.0001
Multivariate-adjusted[a]	0.04 (0.03–0.05)	0.02 (0.02–0.03)	0.059
DBP (mmHg)			
Crude	74.5 (72.6–76.4)	64.0 (62.6–65.3)	<0.0001
Age-adjusted	74.9 (73.0–76.7)	63.8 (62.5–65.1)	<0.0001
Multivariate-adjusted[a]	75.5 (58.4–92.6)	64.0 (47.0–80.9)	<0.0001
Carotid IMT (mm)			
Crude	0.52 (0.50–0.54)	0.55 (0.54–0.56)	0.007
Age-adjusted	0.52 (0.51–0.54)	0.55 (0.53–0.56)	0.027
Multivariate-adjusted[a]	0.51 (0.36–0.66)	0.55 (0.40–0.70)	0.003

BMI body mass index, *T-chol* total cholesterol, *FBS* fasting blood sugar, *CRP* high-sensitivity C-reactive protein, *IMT* intima–media thickness

[a] Adjusted for age, FBS, BMI, IMT, T-chol, DBP and CRP

[b] Geometric mean

Table 2 Comparison of selected characteristics between healthy subjects in the highest quartile of carotid IMT and those in the remaining three quartiles

	Highest quartile[a] ($n = 99$)	Remaining three quartiles ($n = 328$)	P
Age (years)	53.1 (51.4–54.7)	45.0 (44.1–45.9)	<0.001
Male sex, n (%)	70 (70.7)	173 (52.7)	0.002
Prevalence of smokers, n (%)[b]	29 (36.3)	76 (27.4)	0.128
Prevalence of drinkers, n (%)[b]	74 (74.8)	235 (71.9)	0.574
FBS (mg/dl)	102 (94.7–107)	94.8 (92.9–96.7)	0.001
T-chol (mmol/l)	213 (206–221)	203 (199–206)	0.005
HDL-chol (mmol/l)	54.6 (51.9–57.3)	59.3 (57.7–60.9)	0.005
LDL-chol (mmol/l)	133 (126–139)	120 (117–123)	<0.001
Triglycerides (mmol/l)	131 (112–151)	119 (107–130)	0.296
HbA_{1c} (%)	5.14 (4.96–5.33)	4.82 (4.76–4.88)	<0.001
CRP (mg/dl)[c]	0.04 (0.04–0.05)	0.03 (0.03–0.03)	0.001
BMI (kg/m^2)	24.2 (23.5–24.9)	22.2 (21.9–22.6)	<0.001
Body fat (%)	25.2 (24.1–26.3)	24.0 (23.5–24.6)	0.057
DBP (mmHg)	77.1 (68.9–73.4)	66.9 (65.8–68.0)	<0.001
SBP (mmHg)	119 (115–122)	112 (110–113)	<0.001

IMT intima–media thickness, *FBS* fasting blood sugar, *T-chol* total cholesterol, *HbA_{1c}* glycosylated hemoglobin, *CRP* high-sensitivity C-reactive protein, *BMI* body mass index

[a] Mean IMT ≥0.63 mm

[b] Several observations with missing values

[c] Geometric mean

and CRP, SLE patients with the highest SLEDAI (6+) showed a significantly higher carotid IMT [0.57 mm (95 % CI = 0.44–0.68) vs. 0.48 mm (95 % CI = 0.36–0.59)] than patients with the lowest SLEDAI (0–2) ($P = 0.027$, ANCOVA followed by the Bonferroni test). SLEDAI was associated with carotid IMT in a dose-dependent manner ($P_{trend} = 0.041$). SDI was not associated with carotid IMT, however.

The ORs of increased carotid IMT (>0.5 mm, above median) in relation to treatment for SLE are shown in Table 5. Multivariate-adjusted OR of increased carotid IMT for current users of cyclosporine A versus nonuser of cyclosporine A was 0.02 (95 % CI = 0.01–0.40, $P = 0.011$). Similarly, the patients who had a history of steroid pulse therapy revealed a reduced risk of increased carotid IMT (OR = 0.01, 95 % CI = 0.01–0.25, $P = 0.006$). In contrast, current use of NSAIDs was marginally associated with an increased risk of increased carotid IMT (OR = 0.56, 95 % CI = 0.97–32.3, $P = 0.054$). The remaining treatment factors were not associated with the risk of increased carotid IMT.

Table 3 Detailed characteristics of SLE patients

Variable	Mean (range) or *n* (%)
Age (years)	43.74 (18–77)
Age at diagnosis (years)	29.93 (10–68)
Disease duration (years)	14.12 (0–35)
SLEDAI	4.11 (0–16)
SDI	1.08 (0–4)
Cumulative steroid use (g)	128.52 (0–347.48)
Past user of cyclosporine A	18 (19.57)
Current user of cyclosporine A	13 (14.13)
Past user of cyclophosphamide	15 (16.30)
Current user of cyclophosphamide	0 (0.00)
Current user of tacrolimus	8 (8.70)
Current user of statins	26 (28.26)
Current user of NSAIDs	36 (39.13)
Current user of warfarin	15 (16.30)
Current user of CaB	19 (20.65)
Current user of ARBs	23 (25.00)
Having a history of steroid pulse therapy	20 (21.74)

Discussion

The mechanism of accelerated atherosclerosis in SLE is unclear. It is likely to be due to conventional risk factors, factors related to the disease itself and/or treatment factors for SLE. In this study, female SLE patients showed significantly lower BMIs than female healthy controls ($P = 0.004$). Based on data from the National Health and Nutrition Survey in Japan in 2008, the mean BMI among women in their 40s has been reported to be 22.2 [11]. BMI was lower in our healthy controls than in the female general population. Although SLE patients have a higher prevalence of obesity [12], the mean BMI was similar between SLE patients and healthy controls [12, 13]. Although little is known about the effects of obesity in SLE patients, SLE patients were instructed to lose weight because they are at risk of atherosclerosis. As a result, BMI can be decreased in SLE patients. SLE patients showed marginally lower T-chol ($P = 0.064$). This was just as valid for T-chol. Multivariate-adjusted mean of CRP was marginally higher in SLE patients than in healthy controls ($P = 0.064$). It has been reported that modest CRP elevation is common in SLE patients [14].

Table 4 Association between clinical status and carotid IMT

Clinical status	*n*	Mean carotid IMT (95 % CI), mm			
		Crude	*P*	Adjusted[a]	*P*
SLEDAI					
0–2	44	0.49 (0.47–0.52)		0.48 (0.36–0.59)	
3–5	21	0.52 (0.50–0.54)	0.025	0.52 (0.41–0.64)	0.027
6+	27	0.55 (0.52–0.58)		0.57 (0.44–0.68)	
		$P_{trend} < 0.0001$		$P_{trend} = 0.041$	
SDI					
0–1	64	0.51 (0.48–0.53)		0.51 (0.37–0.65)	
2+	28	0.54 (0.51–0.57)	0.070	0.51 (0.37–0.65)	0.719

CI confidence interval, *IMT* intima–media thickness

[a] Adjsuted for age, FBS, BMI, T-chol, DBP and CRP

Table 5 Multivariate-adjusted ORs (95 % CI) of increased carotid IMT (>0.5 mm) in relation to treatment for SLE

Treatment factor	OR (95 % CI)			
	Crude	*P*	Adjusted[a]	*P*
Past use of cyclosporine A				
Positive vs. negative	0.46 (0.16–1.32)	0.147	1.26 (0.19–8.15)	0.811
Current use of cyclosporine A				
Positive vs. negative	0.12 (0.02–0.57)	0.008	0.02 (0.01–0.40)	0.011
Past use of cyclophosphamide				
Positive vs. negative	1.31 (0.43–4.06)	0.632	0.21 (0.02–2.63)	0.226
Current use of tacrolimus				
Positive vs. negative	0.83 (0.19–3.53	0.796	0.69 (0.07–7.22)	0.759
Cumulative steroid use (g)				
>127.75 vs. 0–127.75	2.32 (1.00–5.39)	0.050	2.44 (0.46–12.9)	0.295
Current use of statins				
Positive vs. negative	1.89 (0.74–4.84)	0.185	0.34 (0.04–2.89)	0.321
Current use of NSAIDs				
Positive vs. negative	1.30 (0.56–3.03)	0.539	5.60 (0.97–32.3)	0.054
Current use of warfarin				
Positive vs. negative	0.69 (0.23–2.10)	0.515	0.57 (0.06–4.95)	0.607
Current use of CaB				
Positive vs. negative	2.88 (0.94–8.82)	0.064	1.40 (0.23–8.44)	0.530
Current use of ARBs				
Positive vs. negative	3.09 (1.09–8.77)	0.034	2.04 (0.22–18.9)	0.720
History of steroid pulse therapy				
Positive vs. negative	0.27 (0.09–0.79)	0.017	0.01 (0.01–0.25)	0.006

OR odds ratio, *CI* confidence interval, *IMT* intima–media thickness, *NSAIDs* non-steroidal anti-inflammatory drugs, *CaB* calcium blocker, *AB* angiotensin receptor blockers

[a] Adjusted for age, DBP, BMI, T-chol, CRP and SLEDAI

It is generally accepted that CRP levels less than 0.3 mg/dl (range 0–1 mg/l) are considered normal [14, 15]. Therefore, mean CRP levels of SLE patients remain within the normal range. DBP was significantly higher in SLE patients than in healthy controls ($P < 0.0001$). Based on data from the National Health and Nutrition Survey in Japan in (2008), the mean DBP among women in their 40s has been reported to be 76 mmHg [11]. DBP was somewhat lower in our SLE patients (74.5 mmHg) than in the general female population (76 mmHg). As the means of BMI, T-chol, FBS and DBP were lower in our female controls than in the female general population, our controls (health checkup examinees) are possibly healthier than the general population. Health check examinees are concerned with the maintenance and promotion of their health (self-selection bias). Unexpectedly, carotid IMT was significantly lower in SLE patients compared to healthy controls ($P = 0.003$). As discussed previously, the difference in carotid IMT may become more exaggerated when our SLE patients and female general population are compared. Roman et al. [16] also reported that carotid IMT was significantly less in SLE patients than controls. Some studies reported that SLE patients had a greater carotid IMT than population controls [17–20], while other studies found no significant difference between the two groups [21–25]. A considerable number of factors such as the carotid IMT measurement method, study population characteristics and disease activity may explain this unanticipated discrepant result. In this study, we used a newly developed computer-automated system that provided more accurate IMT data compared to the conventional manual eye-measurement method. Male sex, FBS, HbA_{1c}, T-chol, LDL-chol, triglycerides, CRP, BMI DBP and SBP were significantly related with carotid IMT in 427 healthy controls (Table 2). Similar results have been reported in many studies [26–30], but most of these were reported in populations that included patients with coronary artery disease, hypercholesterolemia, cerebrovascular disease, diabetes mellitus and hypertension. As shown in Table 4, SLEDAI was positively associated with carotid IMT. Carotid IMT is a simple and noninvasive method and is increasingly used as a surrogate marker of atherosclerosis [5]. Atherosclerosis is characterized by infiltration of the intima by activated macrophages and T cells, and it is thus considered to be caused by inflammatory processes [31]. Vasculitis is a common feature of SLE. Deposition of circulating immune complexes in SLE is supposed to lead to the leukocyte adhesion and activation, production of cytokine and other inflammatory mediators [32]. It is therefore conceivable that carotid IMT was increased in SLE patients with higher disease activity, namely with higher SLEDAI. In contrast, accumulated damage in SLE (SDI) was not associated with carotid IMT. Carotid IMT may reflect the current, and not the past, inflammatory status in the vessels.

As shown in Table 5, a history of steroid pulse therapy was associated with decreased carotid IMT. As steroid pulse therapy is given to SLE patients with the most severe disease activity, intensive care and swift disease control of SLE might overcome the possible pro-atherosclerotic effect of prednisolone when the pro-atherosclerotic effect of SLE disease activity is considered. In addition, cumulative steroid use did not have any association with the carotid IMT in our SLE patients. Increased cumulative