Table 1. Distribution of patients in 3 decades from 1974 to 2003

Year	Total no. of patients	No. of smoldering type (% of total)	No. of chronic type (% of total)
1974-1983	19	2 (10.5)	17 (89.5)
1984-1993	35	7 (20.0)	28 (80.0)
1994-2003	36	16 (44.4)	20 (55.6)
Total for all years	90	25 (27.8)	65 (72.2)

was granted an exemption from the institutional review board and waived the requirement for written informed consent.

Clinical factors and definitions

Age was dichotomized into 2 groups: 60 years or older and younger than 60 years. Performance status (PS) was based on the 5-grade scale of the World Health Organization. Complications at diagnosis were dichotomized into present and absent. Leukocytosis was defined as white blood cell count of 12×10^9/L or greater with the median value as cutoff level. Lymphocytosis was defined as a total lymphocyte count of 6.5×10^9/L or greater with the median value as cutoff level. Neutrophilia was defined as a neutrophil count of 7.5×10^9/L or greater.[10] Eosinophilia was defined as an eosinophil count of 0.4×10^9/L greater.[11] Lactate dehydrogenase (LDH) and blood urea nitrogen (BUN) were dichotomized into normal and elevated concentrations.[12] Albumin was dichotomized into concentrations of 40.0 g/L (4.0 g/dL) or greater and less than 40.0 g/L (4.0 g/dL).[2] Potential prognostic factors (PPFs) for chronic ATL were defined as those with at least one of the following 3 factors: low serum albumin, high LDH, or high BUN according to previous reports.[13,14] Tumor lesions were evaluated as the number of lymph node lesions, number of extranodal lesions, and number of total involved lesions. Extranodal lesions were defined as follows: bone marrow (BM) involvement as the presence of more than 5% typical ATL cells on a BM smear or detection of their infiltration in a BM biopsy specimen; skin involvement as the presence of ATL infiltration in a skin biopsy specimen or as the clinically presence of typical types of skin lesions such as tumors, nodules, erythema, and papules, if biopsy was impossible; lung involvement as lesions with ATL cell infiltration in a transbronchial lung biopsy specimen or in bronchoalveolar lavage fluid; liver involvement as hepatomegaly determined by any imaging tests or liver biopsy if done; spleen involvement as splenomegaly on any imaging test. All patients had peripheral blood involvement. Both lymph node and extranodal tumor lesions were determined according to Ann Arbor classification.[2] The number of total involved lesions was defined as the sum of lymph node lesions and extranodal lesions.[2] Factors used in analyses were listed in Table 2.

Statistical analysis

OS was defined as the time from the date of first diagnosis to the date of death or the latest contact with the patient. Survival curves were estimated using the Kaplan-Meier method and were compared using the generalized Wilcoxon test. MST was estimated as the time point at which the Kaplan-Meier survival curves crossed 50%. Time to transformation was calculated as the time from the date of the first diagnosis to the date of transformation into the aggressive type (acute or lymphoma type). Univariate and multivariate Cox regression analyses were applied to evaluate prognostic factors for survival. The effects of clinical parameters were evaluated as hazard ratios (HRs) and their 95% confidence intervals (95% CIs). All statistical analyses were performed using SAS software (Version 9.1; SAS Japan Institute). All tests were 2-tailed, and the statistical significance level was set at .05.

Results

Baseline characteristics

The median value of white blood cell count, lymphocyte count, neutrophil count, and eosinophil count was 11.5×10^9/L (range, 3.9-94.4 $\times 10^9$/L), 6.5×10^9/L (range, 0.9-80.2 $\times 10^9$/L), 4.9×10^9/L (range, 1.5-25.5 $\times 10^9$/L), and 0.06×10^9/L (range, 0-3.0 $\times 10^9$/L), respectively. Frequencies of the patients at baseline are summarized in Table 2. Fifty-eight percent of the patients were male, 52% were 60 years or older, and 22% had an advanced PS (2 or more grade). Regarding complications, 35 patients (39%) had some complications at the time of diagnosis, including 13 with chronic pulmonary diseases (10 chronic bronchitis, 2 diffuse panbronchiolitis, and 1 bronchial asthma with chronic bronchitis), 9 with opportunistic infections (3 pneumocystis pneumonia, 2 cryptococcal meningitis, 2 aspergillus pneumonia, 1 cytomegalovirus infection, and 1 pulmonary tuberculosis), 7 with malignancies other than ATL (2 lung cancer, 1 larynx cancer, 1 pharynx cancer, 1 colon cancer, 1 hepatic cell carcinoma, and 1 lip cancer), and 6 with autoimmune diseases (2 infective dermatitis, 1 primary biliary cirrhosis, 1 autoimmune hemolytic anemia, 1 dermatomyositis, and 1 ulcerative colitis). The 6 patients with autoimmune diseases had received a variety of medications as follows: antibiotics for infective dermatitis, ursodeoxycholic acid for primary biliary cirrhosis, prednisolone for autoimmune hemolytic anemia and dermatomyositis, and sulfasalazine for ulcerative colitis. Concerning the hematologic factors, 43 patients (48%) had leukocytosis, 45 (50%) had lymphocytosis, 17 (19%) had neutrophilia, and 17 (19%) had eosinophilia. Regarding the laboratory factors, 28 patients (31%) had a high LDH level (greater than the normal limit). Only 5 of 87 patients (6%) had an abnormal BUN level; 34 of 88 patients (39%) had a low albumin level. Forty-seven patients (55%) had more than 1 of the 3 unfavorable prognostic factors.

Twenty-four patients (27%) had more than 2 involved lymph node lesions. Regarding the extranodal lesions, skin involvement was observed in 46 patients (51%), liver involvement in 15 (17%), spleen involvement in 6 (7%), and pulmonary involvement in 1 (1%). Of the 64 patients who had BM examined, the involvement was observed in 16 patients (25%; data not shown). Twenty percent of the patients (n = 18) had more than 3 extranodal lesions. Regarding the number of total involved lesions (extranodal lesions plus lymph node lesions), more than 4 involved lesions were observed in 24 patients (27%), 2 or 3 involved lesions in 42 patients (46%), and only 1 involved lesion in 24 patients (27%).

Prognosis

Among 90 patients with indolent ATL, 63 (70%) died, with a median duration of follow-up of 4.1 years (range, 8 days to 17.6 years). The estimated 5-, 10-, and 15-year survival rates were 47.2% (95% CI, 36.1%-57.5%), 25.4% (95% CI, 15.3%-36.8%), and 14.1% (95% CI, 6.2%-25.3%), respectively, with an MST of 4.1 years (95% CI, 2.9-6.3 years; Figure 1A). No plateaus were observed in the survival curves for OS. Of the 27 survivors, 12 were alive for more than 10 years. Of the 63 patients who died, 41 (65.1%) died of acute ATL after transformation, 5 (7.9%) died of severe chronic ATL, 11 (17.5%) died of other diseases (3 malignancies other than ATL, 2 chronic pulmonary diseases, 2 opportunistic infections, 2 autoimmune diseases, 1 cardiac failure, and 1 myocardial infarction), 2 died of transplantation-related complications, and 4 died of unknown cause. No significant difference in OS was observed between patients who died of ATL and patients who died of other causes (data not shown). Among 90 patients, 44 (49%) progressed to aggressive ATL (all were acute types), among those, 41 (93%) died. The median time to transformation was 18.8 months (range, 0.3 months to 17.6 years).

Table 2. Survival by baseline clinical factors

Factors	No. of evaluated (% of total)	No. of deaths (%)*	MST, y	Cumulative probability of survival†		
				5-y survival, % (95% CI)	10-y survival, % (95% CI)	P†
Total	90	63 (70)	4.1	47.2 (36.1-57.5)	25.4 (15.3-36.8)	
Clinical subtype						
Smoldering	25 (28)	17 (68)	2.9	39.4 (19.8-58.6)	25.3 (8.2-47.0)	.36
Chronic	65 (72)	46 (71)	5.3	50.2 (37.0-62.0)	26.3 (14.6-39.5)	
Patient-related factors (n = 90)						
Sex						
Male	52 (58)	34 (65)	4.3	48.1 (33.4-61.3)	24.9 (11.8-40.5)	.99
Female	38 (42)	29 (76)	4.1	46.4 (29.5-61.6)	26.5 (12.0-43.4)	
Age						
60 y or older	46 (52)	32 (70)	3.7	45.5 (30.4-59.4)	29.5 (14.8-45.8)	.18
Younger than 60 y	44 (48)	31 (70)	4.5	49.2 (32.9-63.6)	24.0 (11.2-39.3)	
PS						
0	22 (24)	15 (68)	8.4	75.9 (51.4-89.1)	38.9 (16.8-60.7)	.006
1	49 (54)	33 (67)	3.4	41.5 (26.9-55.5)	22.5 (9.7-38.5)	
2 or 3	19 (22)	15 (79)	1.3	27.9 (10.2-49.0)	13.9 (1.3-41.1)	
Complications at diagnosis (n = 90)						
Absent	55 (61)	37 (67)	5.7	54.1 (39.4-66.7)	25.4 (12.9-40.1)	
Present	35 (39)	26 (74)	3.4	36.6 (20.7-52.8)	28.3 (13.5-45.1)	.06
Malignancies other than ATL	7 (8)	6 (86)	0.8	28.6 (4.1-61.2)	28.6 (4.1-61.2)	
Opportunistic infection	9 (10)	7 (78)	1.2	0	0	
Chronic pulmonary disease	13 (14)	10 (77)	4.1	38.5 (14.1-62.8)	25.6 (5.2-53.4)	
Autoimmune disease	6 (7)	3 (50)	11.4	62.5 (14.2-89.3)	62.5 (14.2-89.3)	
Hematologic factors						
WBC count (n = 90)						
At least 12.0 × 10^9/L	43 (48)	32 (74)	3.4	43.0 (27.6-57.5)	22.3 (9.9-37.8)	.24
Less than 12.0 × 10^9/L	47 (52)	31 (66)	5.3	51.0 (35.1-64.8)	28.5 (13.6-45.2)	
Total lymphocyte count (n = 90)						
At least 6.5 × 10^9/L	45 (50)	35 (78)	3.7	43.3 (28.2-57.5)	17.4 (6.8-32.0)	.34
Less than 6.5 × 10^9/L	45 (50)	28 (62)	5.3	51.4 (35.2-65.4)	36.8 (20.9-52.9)	
Neutrophil counts (n = 89)						
At least 7.5 × 10^9/L	17 (19)	14 (82)	2.3	29.4 (10.7-51.1)	14.7 (1.3-42.9)	.05
Less than 7.5 × 10^9/L	72 (81)	48 (67)	5.3	51.0 (38.3-62.4)	28.4 (16.6-41.3)	
Eosinophil count (n = 89)						
At least 0.4 × 10^9/L	17 (19)	11 (65)	4.0	34.9 (13.0-58.0)	23.2 (4.9-49.4)	.47
Less than 0.4 × 10^9/L	72 (81)	51 (71)	4.5	49.2 (36.8-60.5)	27.4 (16.0-40.1)	
Laboratory factors						
LDH (n = 90)						
Greater than NI	28 (31)	23 (82)	1.5	34.8 (17.3-53.0)	14.9 (3.9-32.7)	.004
Less than or equal to NI	62 (69)	40 (65)	5.4	52.9 (39.2-64.8)	31.8 (18.5-45.9)	
BUN (n = 87)						
Greater than NI	5 (6)	5 (100)	2.0	20.0 (0.8-58.2)	0	.18
Less than or equal to NI	82 (94)	56 (68)	4.5	48.9 (37.2-59.6)	28.4 (17.3-40.6)	
Albumin (n = 88)						
Less than 40.0 g/L	34 (39)	22 (65)	3.4	39.9 (22.4-56.8)	25.6 (8.9-46.4)	.22
At least 40.0 g/L	54 (61)	40 (74)	5.3	52.2 (37.9-64.7)	26.6 (14.3-40.6)	
Potential prognostic factors (n = 87)‡						
At least 1	47 (55)	34 (72)	2.9	38.7 (24.1-53.1)	18.1 (6.5-34.3)	.05
None	40 (45)	27 (68)	5.4	56.1 (39.2-70.0)	35.2 (19.3-51.6)	
Tumor lesions (n = 90)						
No. of lymph node lesions						
2 or more	24 (27)	16 (67)	2.1	37.5 (19.0-56.0)	30.0 (12.1-50.4)	.09
0 or 1	66 (73)	47 (71)	5.3	50.9 (37.5-62.8)	23.6 (12.2-37.2)	
No. of extranodal lesions						
3 or more	18 (20)	14 (78)	1.1	29.4 (10.7-51.1)	19.6 (4.2-43.3)	.005
1 or 2	72 (80)	49 (68)	5.3	51.6 (38.9-62.9)	26.8 (15.2-39.7)	
No. of total involved lesions						
4 or more	24 (27)	16 (67)	1.3	34.8 (16.6-53.7)	26.1 (8.8-47.6)	.03
2 or 3	42 (46)	30 (71)	4.5	49.5 (32.7-64.3)	13.1 (3.5-29.1)	
1	24 (27)	17 (71)	5.4	54.5 (32.1-72.4)	44.1 (22.8-63.5)	
Chemotherapy						
Received	12 (13)	12 (100)	1.4	25.0 (6.0-50.5)	0	.01
Not received	78 (87)	51 (65)	5.3	50.8 (38.6-61.8)	31.3 (19.3-44.0)	

WBC indocates white blood cell count; MST, median survival time (years); and NI, normal index.

*Rate of death in evaluated cases.

†Cumulative probability of survival rate was estimated with the Kaplan-Meier method, and the *P* value was calculated with the generalized Wilcoxon test.

‡PPFs indicate at least 1 of the following 3 factors: low serum albumin, high LDH, or high BUN.[13,14]

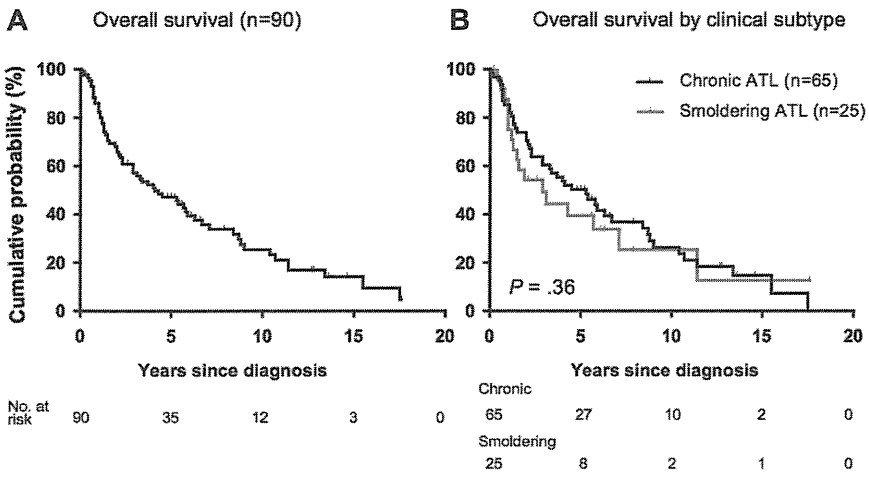

Figure 1. Survival of patients with indolent ATL. (A) For OS (n = 90), the median survival time was 4.1 years (95% CI, 2.9-6.3 years). No plateau was observed in the survival curves for OS. The estimated 5-, 10-, and 15-year survival rates were 47.2% (95% CI, 36.1%-57.5%), 25.4% (95% CI, 15.3%-36.8%), and 14.1% (95% CI, 6.2%-25.3%), respectively. (B) OS by clinical subtype (smoldering type vs chronic type). The estimated 15-year survival rate was 12.7% (95% CI, 1.1%-38.8%) with an MST of 2.9 years for smoldering type and 14.7% (95% CI, 5.7%-27.8%) with an MST of 5.3 years. There was no statistically significant difference ($P = .36$).

Among 25 patients with smoldering ATL, 17 patients (68%) died, and the estimated 15-year survival rate was 12.7% (95% CI, 1.1%-38.8%) with an MST of 2.9 years (95% CI, 1.3-7.1 years). Of the 17 patients who died, 15 died of acute ATL after transformation. Among 65 patients with chronic ATL, 46 (71%) died, and the estimated 15-year survival rate was 14.7% (95% CI, 5.7%-27.8%) with an MST of 5.3 years (95% CI, 2.9-6.7 years). Of the 46 patients who died, 29 died of acute ATL after transformation and 5 died of the disease severity. No statistically significant difference was observed in OS between subtypes ($P = .36$; Figure 1B). The overall estimated 5- and 10-year survival rates of both subtypes are shown in Table 2.

Effects of clinical factors on prognosis

Effects of clinical factors on prognosis were analyzed with the use of all the 90 patients together. Results of prognostic analyses (estimated 5- and 10-year OS rates and MST) with the use of Kaplan-Meier methods are summarized in Table 2. The survival rate was poor for patients with advanced PS ($P = .006$; Figure 2A), neutrophilia ($P = .05$; Figure 2B), and a higher LDH level ($P = .004$; Figure 2C). Patients with at least 1 of 3 PPFs for chronic ATL (a high level of LDH and BUN and a low level of albumin)[13,14] showed a poor survival rate compared with patients without ($P = .05$; Figure 2D). The difference in survival rates between patients with any complications and patients without was marginally significant ($P = .06$). Among patients with any complications, those with malignancies other than ATL or opportunistic infections at diagnosis showed a tendency of poor prognosis, although the number of patients in each category was too small (supplemental Figure 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Although no difference was observed in survival rates between patients with involvement of more than 2 lymph node lesions and patients with less involvement ($P = .09$; Table 2), the survival rate of patients

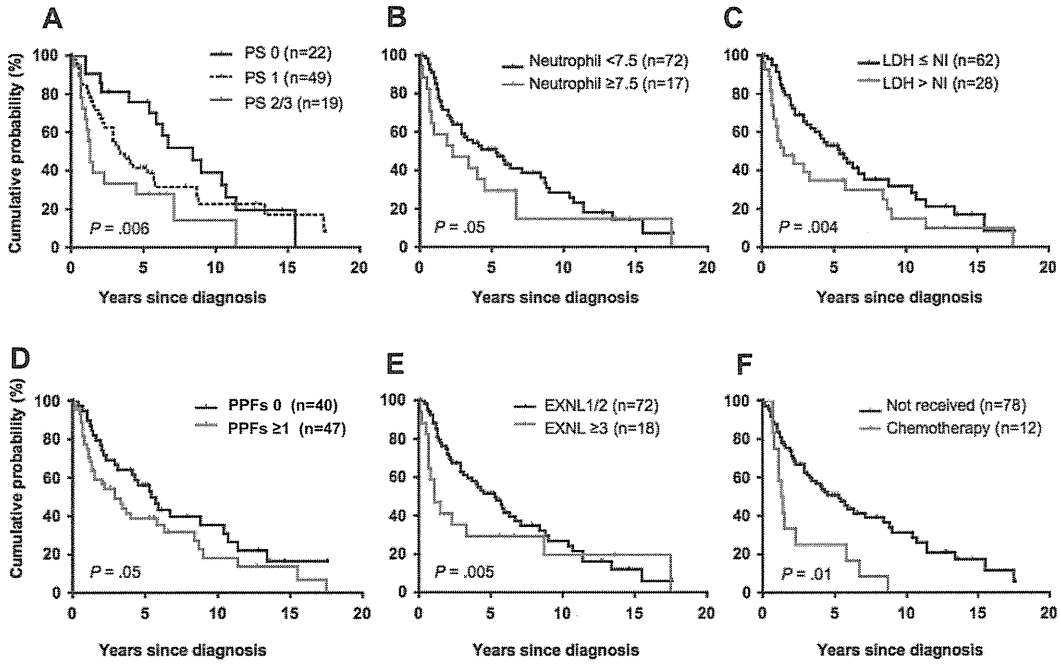

Figure 2. OS by clinical parameters. (A) OS by PS ($P = .006$). (B) OS by neutrophil count ($P = .05$). The unit is $\times 10^9$/L. (C) OS by LDH level ($P = .004$). NI indicates normal index. (D) OS by PPFs for chronic ATL that were defined based on low serum albumin, high LDH, or high BUN according to previous reports[13,14] ($P = .05$). (E) OS by the number of extranodal lesions (EXNL; $P = .005$). (F) OS by treatment states ($P = .01$).

Table 3. Effects of clinical factors on OS in Cox analyses

	All patients (n = 90)						Patients had not received chemotherapy (n = 78)					
	Univariate analysis		Multivariate model A		Multivariate model B		Univariate analysis		Multivariate model C		Multivariate model D	
Clinical factor	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
PS												
0	1		1		1		1		1		1	
1	1.5 (0.8-2.7)	.22	1.4 (0.8-2.8)	.27	1.3 (0.7-2.6)	.37	1.4 (0.7-2.7)	.28	1.6 (0.8-3.1)	.21	1.4 (0.7-2.9)	.30
2 or more	2.5 (1.2-5.2)	.01	2.1 (1.0-4.6)	.06	2.1 (1.0-4.6)	.06	1.7 (0.7-4.0)	.26	1.5 (0.6-3.8)	.39	1.6 (0.6-4.2)	.30
Neutrophil counts												
Less than 7.5 × 10^9/L	1		1		1		1		1		1	
7.5 × 10^9/L or greater	1.6 (0.9-2.9)	.15	1.3 (0.6-2.7)	.45	1.2 (0.6-2.3)	.58	1.3 (0.6-2.7)	.47	1.5 (0.6-3.8)	.43	1.0 (0.5-2.3)	.94
LDH												
Less than or equal to NI	1		1		1		1		1		1	
Greater than NI	1.7 (1.0-2.9)	.04	1.5 (0.8-2.7)	.16	1.5 (0.8-2.6)	.21	1.5 (0.8-2.8)	.19	1.7 (0.9-3.3)	.12	1.6 (0.8-3.1)	.20
No. of extranodal lesions												
0-2	1		1				1		1			
3 or more	1.5 (0.8-2.8)	.16	0.7 (0.3-1.6)	.41			0.9 (0.4-2.2)	.82	0.5 (0.1-1.6)	.22		
No. of total involved lesions												
1	1				1		1				1	
2 or 3	1.2 (0.7-2.2)	.52			0.8 (0.4-1.6)	.52	1.1 (0.6-2.1)	.67			0.9 (0.4-1.7)	.65
4 or more	1.5 (0.7-3.0)	.26			0.9 (0.4-2.1)	.83	1.0 (0.5-2.3)	.96			0.8 (0.3-2.0)	.67
Chemotherapy												
Not received	1		1		1							
Received	2.6 (1.4-5.1)	.003	2.3 (1.1-4.7)	.03	2.0 (1.0-4.2)	.06						

HR indicates hazard ratio; 95% CI, 95% confidence interval; and NI, normal index.

with more than 3 extranodal lesions was significantly poor than the others ($P = .005$; Figure 2E). The survival rate was worse in patients with more than 4 total involvement lesions than in the others (Table 2). Of the extranodal lesions, we additionally examined the effect of skin lesion and BM involvement on survival rates. The survival rate of patients with BM involvement was significantly poor than of patients without ($P = .04$; data not shown), but that of patients with skin involvement was not different from those without ($P = .66$; supplemental Figure 2).

Although most patients in this study had not been treated until their disease progression was similar to B-cell chronic lymphoid leukemia, 12 patients with chronic ATL were treated with chemotherapy immediately after diagnosis because of elevated LDH levels in 8 patients, severe BM involvement in 2 patients, and severe skin involvements in 2 patients. Among them, 2 patients were treated with VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone)–AMP (doxorubicin, ranimustine, and prednisone)–VECP (vindesine, etoposide, carboplatin, and prednisone),[3] 2 with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), 4 with CHOP-like, 3 with VEPA (vincristine, etoposide, prednisone, and doxorubicin),[15] and 1 with low-dose etoposide. All of these patients died (MST, 1.4 years; 95% CI, 1.1-2.3 years), and their prognosis was very poor compared with patients not treated ($P = .01$; Figure 2F).

On the basis of results from Kaplan-Meier curves and univariate analysis for each factor, we decided to include PS category, dichotomized neutrophil counts, dichotomized LDH category, dichotomized number of extranodal lesions, the number of total involved lesions, and chemotherapy states into multivariate Cox analysis. Model A included PS category, dichotomized neutrophil counts, dichotomized LDH category, dichotomized number of extranodal lesions, and chemotherapy states. Model B included the same factors as model A except for the number of total involved lesions instead of the number of extranodal lesions. This was because, by definition, a factor of the number of total involved lesions included a factor of the number of extranodal lesions. Results were summarized in Table 3. In model A, advanced PS (≥ 2; HR, 2.1; 95% CI, 1.0-4.6; $P = .06$, borderline significance) and chemotherapy states (HR, 2.3; 95% CI, 1.1-4.7; $P = .03$, significance) were correlated with OS, but the remaining factors were not independent prognostic factors after adjustment for covariate factors. To evaluate effects of clinical factors beyond the effect of chemotherapy states on OS, we also performed additional multivariate analyses for patients who were not received chemotherapy (n = 78; model C and model D in Table 3). We found that there was no clinical parameter that associated with OS.

Discussion

In the present study, we investigated for the first time the long-term clinical course of patients with indolent ATL with a maximum duration of follow-up of 17.6 years. We found that the prognosis of indolent ATL was poor with the MST of 4.1 years, and the estimated 15-year OS rates were 14.1% with no plateau in the survival curve. The prognosis observed in the present study was poorer than expected. Our results confirmed a recent long-term Brazilian study,[6] that showed a poor OS of less than 20% for indolent ATL. In the present study, we showed that 65.1% of patients died of acute ATL with a median time to transformation of 18.8 months. This finding suggests that most patients with indolent ATL will eventually die of aggressive ATL during their long-term course of illness. These findings suggest that even patients with indolent ATL should be carefully observed by frequent clinical visits.

The cause of death in patients with indolent ATL has not been well reported so far. In the present study, patients with indolent ATL died of various causes such as malignancies other than ATL,

chronic pulmonary diseases, opportunistic infections, and autoimmune diseases, in addition to death from acute ATL after transformation. A previous long-term study, which followed-up 50 HTLV-1 carriers with monoclonal proliferation of T lymphocytes (pre-ATL) for 20 years, also reported that 10 patients died of opportunistic infections such as *Pneumocystis* pneumonia or malignancies other than ATL (skin carcinoma, lung cancer, etc).[16] Patients with indolent ATL were also comorbid with a variety of diseases at diagnosis such as chronic pulmonary disease, opportunistic infections, multiple cancers, and autoimmune diseases in the present study. The pathogens responsible for the opportunistic infections were similar to those observed in patients with AIDS associated with HIV. Opportunistic infection was previously reported as a frequent complication in patients with aggressive or with indolent ATL.[2] These findings suggest that helper T-cell function in indolent ATL might be impaired similar to that in AIDS.[17]

We also presented that chronic pulmonary disease, multiple cancers, and autoimmune diseases were frequent as complications at diagnosis in indolent ATL. The reason why indolent ATL had such immune dysregulation remains unknown. It was recently noted that the origin of the ATL cells in a fraction of the patients was from regulatory T cells expressing FoxP3 and CCR4.[18,19] In the present study, 6 patients also had autoimmune diseases. Among them, 3 patients were treated with immunosuppressive drugs, and of those only one patient with smoldering ATL transformed to acute ATL. Therefore, we were not able to evaluate the effect of comorbid autoimmune diseases and immunosuppressive drug therapy on the risk of transformation or poor prognosis so far. Further studies are warranted to elucidate the mechanisms responsible for the development of hyperimmunity or hypoimmunity in patients with indolent ATL.

Although comparison on OS by subtype is not a primary purpose of this study, it was unexpected that survival rates of smoldering ATL (15-year OS, 12.7%) tended to be lower than chronic ATL (15-year OS, 14.7%), and the MST of smoldering ATL (2.9 years) tended to be shorter than chronic ATL (5.3 years; Table 2; Figure 1B). Transformation rates of smoldering ATL and chronic ATL were 60% (n = 15) and 44% (n = 29), respectively (data not shown), which was also unexpected. Although there was no statistically difference in OS, MST, and transformation rate between the 2 groups, our results were different from a previous short-time follow-up study reported by Shimoyama et al[2] (the 4-year survival rates for smoldering type was 62.8%). It was unknown why the rate of smoldering type was poorer than chronic type in the present study. Some previous studies suggested that skin involvements might be a risk factor for poor prognosis of smoldering ATL.[6,20-22] In the present study, the frequency of patients with skin lesion was a little higher in smoldering ATL (n = 14; 56%) than in chronic ATL (n = 32; 49%). The OS of smoldering ATL with skin lesion was worse than that of chronic ATL without skin lesion (supplemental Figure 2), although there was no statistical difference ($P = .5$). Therefore, a possible explanation might be that smoldering ATL with poor conditions (eg, skin involvement) might be disproportionately included in the present study because data were collected at a university hospital, where more advanced cases were referred from city clinics. Another possible explanation might be that the percentage of patients with smoldering-type ATL has increased recently, as shown in Table 1. In recent decades, more patients have been diagnosed with the smoldering type of ATL on the basis of a health examination, including a blood cell count. Some of these patients may have been in the early phase of acute ATL.

Shimoyama et al[2] reported that involved lymph node lesions, extranodal lesions, and total involvement lesions were significantly poor prognostic factors for ATL all together, and low serum albumin, high LDH, or high BUN levels were PPFs for chronic ATL.[13,14] As we expected, patients with at least 1 of 3 known PPFs for chronic ATL (a high level of LDH and BUN and a low level of albumin)[13,14] showed a poor survival rate than patients without (Table 2; Figure 2D). We also confirmed the difference was seen when analyses were performed for chronic ATL only ($P = .03$) but was not seen for smoldering ATL only ($P = .62$; supplemental Figure 3). This suggests that there may be different prognostic factors for smoldering ATL and chronic ATL, respectively. Further detailed studies regarding prognostic factors are needed for individual subtype.

Other than the known 3 potential prognostic factors, an advanced PS, neutrophilia, more than 3 extranodal lesions, more than 4 total involved lesions, and having received chemotherapy were shown to be possible unfavorable prognostic factors for indolent ATL in our Kaplan-Meier analyses (Table 2; Figures 1B, 2A-F). However, in multivariate Cox analyses, only advanced PS and chemotherapy state were associated with OS after adjustment for other covariates (models A and B in Table 3). The poor prognosis in patients with indolent ATL who were treated by chemotherapy was similar to that of the patients with unfavorable chronic ATL who were treated with intensive combination chemotherapy in several clinical trials in Japan.[3,5,23] Although advanced PS was a borderline significant independent poor factor on survival for indolent ATL in the model that used all patients, the factor was not a prognostic factor anymore when data were limited for only untreated patients (models C and D in Table 3). Among 12 patients who received chemotherapy, 7 (58%) had advanced PS at diagnosis. This suggests that patients with advanced PS at diagnosis might have a condition that required treatments, which introduced the disappearance of the effect of advanced PS on survival, even though advanced PS was an independent poor factor.

Regarding the effect of the presence of extranodal lesions on poor survival, we previously reported that BM involvement was a prognostic factor for aggressive ATL.[24] Although we did not present the effect of each extranodal lesion on survival in detail, we also confirmed that the survival rate of patients with BM involvement was significantly poor compared with patients those without BM involvement ($P = .04$; data not shown), but the survival rate of patients with skin involvement was not different compared with those without ($P = .66$; supplemental Figure 2). However, some studies reported that the presence of skin lesions was a possible poor prognostic factor in indolent ATL,[6,20-22] as described earlier. Setoyama et al[21] reported that smoldering cases with a deeper infiltration pattern had a more aggressive course than cases with a superficial infiltration pattern. Degree of skin involvement might be associated with prognosis in indolent ATL.

Previously, our study group noted that some patients showed alterations in tumor suppressor genes (p16 INKA[25,26] or p53[27]) or aneuploidy greater than 1 chromosomal locus by comparative genomic hybridization in ATL cells[28] and that such abnormalities were associated with a poor prognosis. Although we could not perform molecular analyses for all patients in the present study, 7 were examined molecularly, and at least one abnormality was found in each patient (data not shown). They had a poor prognosis and died within 2.5 years. Patients with a poor prognosis who died during the first steep slope in the survival curve (Figure 1A) might have had such genetic alterations.

The primary purpose of this study was to analyze prognosis of smoldering and chronic types together as an indolent type of ATL. Therefore, we were not able to present in detail the difference in

prognostic factors between subtypes, which is one of the limitations in this study. The number of cases evaluated in this study was too small to perform detail analyses for prognostic factors in indolent ATL. Further large-scaled studies are warranted.

In conclusion, the long-term prognosis of patients with indolent ATL was not good without a plateau phase in the survival curve. Further studies are warranted to elucidate patients with indolent ATL who require intensive chemotherapy, allogenic hematopoietic stem cell transplantation (in cases of aggressive ATL), or combination therapy with zidovudine and interferon alfa.[29,30] In addition, new molecular targeting treatments, such as histone deacetylase inhibitors,[31] which have shown promise in the treatment of $CD4^+$ cutaneous T-cell lymphoma, should be taken into consideration for treatment of indolent ATL.

Acknowledgments

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Authorship

Contribution: Y.T. collected and analyzed the data and wrote the manuscript; M.I. analyzed the data and wrote the manuscript; Y.I., M.T., T.J., T.K., Y.Y., S.K., S.I., Y.M., and M.T. made the diagnoses and treated the patients with ATL; and K.T. organized the study.

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CORRESPONDENCE

Is Zidovudine and Interferon-Alfa the Gold Standard for Adult T-Cell Leukemia-Lymphoma?

TO THE EDITOR: Bazarbachi et al[1] recently reported the results of a meta-analysis on the use of zidovudine (AZT) and interferon-alfa (IFN) in adult T-cell leukemia-lymphoma (ATL). They performed a retrospective survey of 254 patients treated at several institutes in which AZT/IFN has been routinely used for the treatment of ATL, and compared the overall survival (OS) between patients who received first-line AZT/IFN and those who received conventional chemotherapy. On the basis of the obtained data, they concluded that AZT/IFN should be considered the gold standard of first-line therapy for leukemic ATL because of better OS in patients with acute, chronic, and smoldering ATL treated by first-line AZT/IFN than chemotherapy.

This treatment approach has not been extensively evaluated in Japan, a major endemic area for ATL, mainly because of the lack of approval of both agents for the treatment of ATL under national health insurance. Therefore, the promising results involving a large number of patients encourage us to perform prospective clinical trials in Japan.

Several points should be taken into consideration when interpreting the Bazarbachi et al[1] data. Most important, the characteristics of patients treated with the two first-line treatment modalities, AZT/IFN and conventional chemotherapy, appear to be similar; however, the decision process to select the therapeutic modality for each patient should be described in more detail to make relevant comparisons. Second, the reasons a fraction of patients treated with conventional chemotherapy subsequently received maintenance AZT/IFN should be described. In addition, the possibility of interference with OS by second-line chemotherapy following AZT/IFN, and by allogeneic hematopoietic stem-cell transplantation, which is considered one of the recommended options for younger patients[2] following either AZT/IFN or chemotherapy, should be discussed.

We reported the results of a multi-institutional phase II study, Japan Clinical Oncology Group (JCOG) 9303, of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etoposide, carboplatin, and prednisone), in which the median survival time (MST) in 56 patients with acute ATL was 10.9 months.[3] The results were similar in the subsequent phase III study, JCOG 9801; MST and 3-year OS were 12.7 months and 23%, respectively (unpublished data). On the other hand, the MST in patients with acute ATL treated with AZT/IFN and chemotherapy was 9 and 6 months, respectively.[1] It should be noted that the MST achieved by chemotherapy and by AZT/IFN reported by Bazarbachi et al appears worse than in the JCOG chemotherapy studies, although there is a possible bias of patients presenting with a more favorable condition in the phase III study, partly because of the eligibility criteria for prospective clinical trials.

On the other hand, the Bazarbachi et al[1] results with AZT/IFN in patients with smoldering and chronic (ie, indolent) ATL are promising in view of potentially establishing a new effective ATL treatment. We recently reported a 5-year OS of as low as 47.2% in patients with indolent ATL who were mainly observed by a watchful waiting policy until disease progression.[4] Surprisingly, Bazarbachi et al[1] reported 100% OS beyond 5 years; however, the number of patients with indolent ATL in their study (n = 17) was too small to conclude that AZT/IFN is the standard of care in this cohort. Furthermore, the reasons some patients received first-line chemotherapy instead of AZT/IFN or watchful waiting should be described more precisely, and a comparison with the OS in patients who had been observed without intervention until progression should be included.

Considering the promising but preliminary nature of the Bazarbachi et al[1] findings, we are now planning a randomized phase III study that compares the outcome of AZT/IFN versus watchful waiting in patients with indolent ATL in Japan. This study will seek to establish the standard of care for patients with indolent ATL in the near future.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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III. リンパ腫の治療　治療各論

成人T細胞白血病・リンパ腫

塚崎邦弘

Adult T cell leukemia-lymphoma (ATL)

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Abstract

Adult T-cell leukemia-lymphoma (ATL) is a distinct malignancy of CD4+/CD25+/CCR4+/FoxP3+ or − Treg/TH2 cells etiologically associated with human T-cell lymphotropic virus type I (HTLV-1). ATL is a single HTLV-1 disease entity with diverse molecular features. Also, the clinical features and prognosis are diverse leading to subtype-classification into acute, lymphoma, chronic, and smoldering types defined by organ involvement, and LDH and calcium values. In case acute, lymphoma or unfavorable chronic subtypes (aggressive ATL), and favorable chronic or smoldering ATL (indolent ATL), intensive chemotherapy followed by allo-HSCT and watchful waiting until disease progression has been recommended, respectively in Japan. Several new agent-trials for ATL are ongoing and in preparation, including a defucosylated humanized anti-CC chemokine receptor 4 monoclonal antibody, IL2-fused with diphtheria toxin, histone deacetylase inhibitors, a purine nucleoside phosphorylase inhibitor, a proteasome inhibitor and lenalidomide.

Key words: ATL, HTLV-1, clinical subtype classification, stratified treatment

はじめに

成人T細胞白血病・リンパ腫(ATL)は，レトロウイルスのhuman T-lymphotropic virus type I(HTLV-1)が染色体DNAにプロウイルスとして単クローン性に組み込まれている成熟T細胞白血病・リンパ腫であり，HTLV-1のendemic area(西南日本沿岸地域，中南米，アフリカなど)出身の成人(日本での発症年齢の中央値は約70歳，30歳未満での発症はまれ)に好発する[1,2]．リンパ節腫脹，肝脾腫，皮膚浸潤が多く，消化管，肺，腎，中枢神経，骨などに浸潤する場合もある．よく合併する高カルシウム血症や日和見感染症が更に症状を多彩にする．くすぶり型や慢性型は，検診などで末梢血液像異常により発見される場合も多い．白血化した急性型，慢性型，くすぶり型では末梢血に，リンパ腫型ではリンパ節に，花弁状の核をもつATL細胞を認める．血清LDH，Caや可溶性IL2受容体はATLの病勢を示すよいマーカーである．抗HTLV-1抗体が陽性であり，ATL細胞は活性化した成熟TH2/制御性T細胞の表面形質(CD3+，CD4+，CD8−，CD25+，CCR4+，FoxP3+ or −，TdT−)を有する成熟T細胞腫

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0047-1852/14/¥60/頁/JCOPY

表1 ATL病型診断規準(文献[9]より改変)

	くすぶり型	慢性型	リンパ腫型	急性型
抗HTLV-1抗体	+	+	+	+
リンパ球数($\times10^3$/mm^3)[*1]	<4	≧4	<4	
異常リンパ球数[*2]	≧5%[*4]	+[*5]	≦1%	+[*5]
flower cell	[*3]	[*3]	no	+
LDH	≦1.5N	≦2N		
補正Ca値(mg/dL)	<11.0	<11.0		
組織学的に腫瘍病変が確認されたリンパ節腫大	no		+	
腫瘍病変				
皮膚	[*4]			
肺	[*4]			
リンパ節	no		yes	
肝腫大	no			
脾腫大	no			
中枢神経	no	no		
骨	no	no		
胸水	no	no		
腹水	no	no		
消化管	no	no		

空欄はほかの病型で規定される条件以外の制約はないことを示す.
N: 正常値上限.
[*1]正常リンパ球と異常リンパ球を含むリンパ球様細胞の実数の和.
[*2]形態学的に明らかなATL細胞.
[*3]ATLに特徴的なflower cellが認められてもよい.
[*4]末梢血中の異常リンパ球が5%未満でくすぶり型と診断されるには,皮膚あるいは肺に組織学的に腫瘍病変が確認されることが必要である.
[*5]末梢血中の異常リンパ球が5%未満で慢性型または急性型と診断されるには,組織学的に腫瘍病変が確認されることが必要である.

瘍である[2,3]. 以上より典型例の診断は容易である. 非典型例では, ATL細胞DNAにHTLV-1遺伝子の単クローン性組み込みを証明して確定診断する.

1. ATLの予後因子, 病型分類, リスクグルーピング

予後因子としては, 1990年代の800例を超える全国調査で年齢, 全身状態(PS), 総病変数, 高Ca血症, 高LDH血症が重要と報告された. 予後因子解析と臨床病態の特徴から, 白血化, 臓器浸潤, 高LDH血症, 高Ca血症の有無と程度により表1, 図1のように病型分類が提唱され, 生存期間中央値(MST)は急性型6カ月, リンパ腫型10カ月, 慢性型24カ月, くすぶり型では3年以上であった[4].

最近, 日本全国の調査で2000-10年に診断された急性型とリンパ腫型ATLの807例を解析し, 予後予測モデルが提唱された. An Arbor臨床病期, PS, 年齢, アルブミン, 可溶性IL2受容体の5因子の多寡により3群に分けられ, そのMSTは高, 中, 低リスク群でそれぞれ4.6, 7.3, 16.2カ月であった(図2)[9]. 一方Japan Clinical Oncology Group(JCOG)のリンパ腫グループ(LSG)(JCOG-LSG)によるアグレッシブATLに対する3つの臨床試験(JCOG9109, 9303, 9801)に登録された276例の解析ではPSと高Ca血症による組み合わせで2群に分けられ, そのMSTは6.3カ月と17.8カ月であった[6]. 前者は後方視的に各施設のすべての患者, 後者は前向き臨

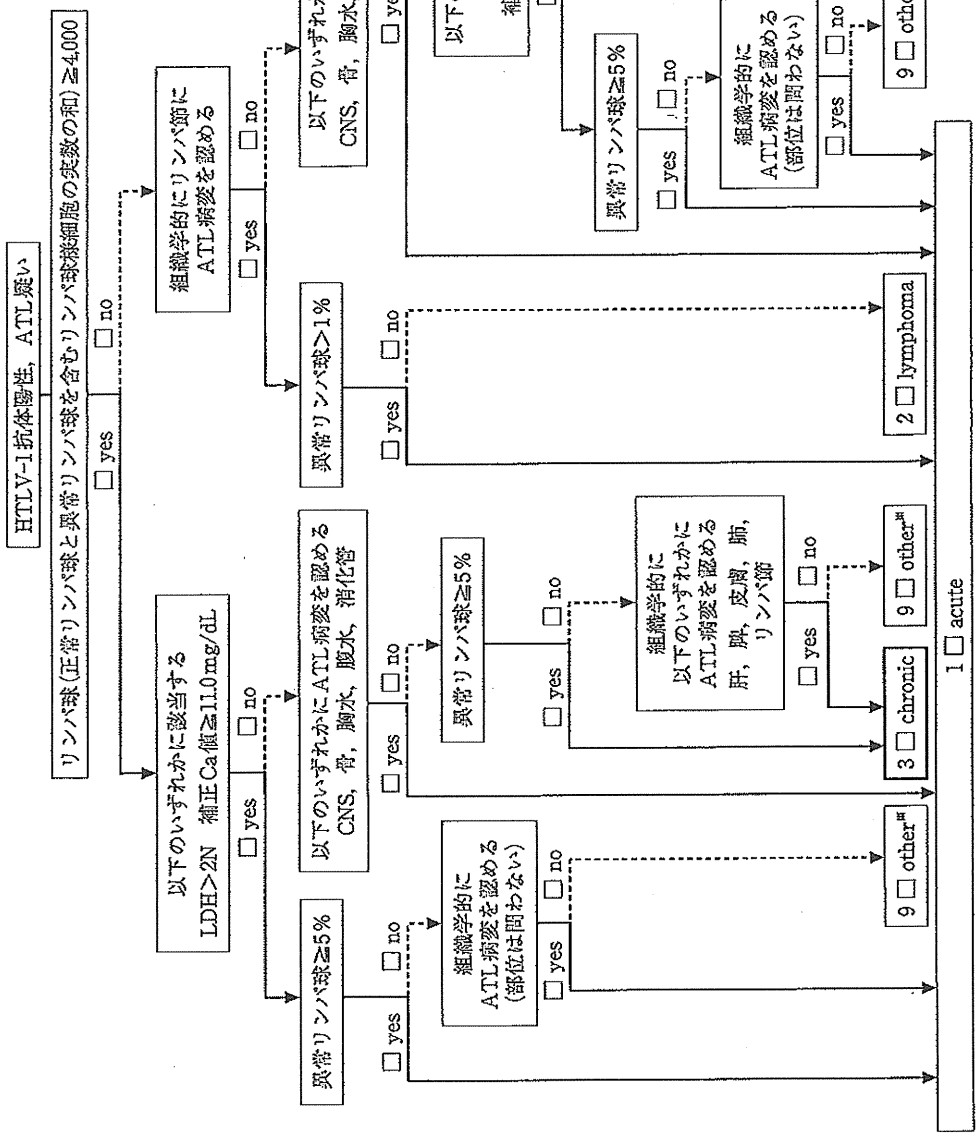
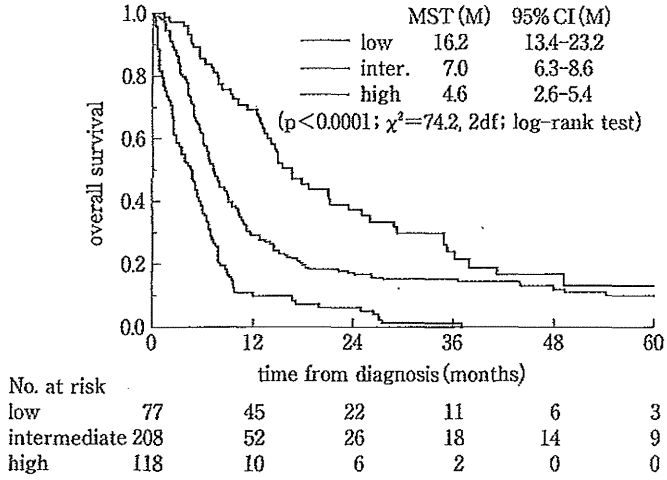


図1　ATL病型診断のフローチャート

高Ca血症：≧11.0 mg/dL.

*該当する場合は，ATL以外の疾患やHTLV-1キャリアの可能性を検討する．



prognostic factor		score
stage	III or IV	2
age (year)	>70	1
serum albumin (g/dL)	<3.5	1
ECOG PS	2-4	1
sIL-2R (U/mL)	>20,000	1

sum of the scores
0・1・2 ⇒ low risk
3・4 ⇒ intermediate risk
5・6 ⇒ high risk

図2 急性型・リンパ腫型ATLの予後予測モデル：2000-09年の後方視的全国調査(文献[9]より改変)

床試験に参加した年齢，臓器予備能などの適格患者で同定されたが，いずれもvalidation setを用いてその有用性が確認されている．しかしながら両予後予測モデルともに予後良好群においてもその5年生存割合は15％未満であることから，例えば'同種造血幹細胞移植療法(allo-HSCT)のような毒性は高いが治癒が望める治療法の候補ではない患者群'を抽出できてはいない．

2. ATLに対する層別化した治療法の開発

急性型やリンパ腫型はCHOP療法などに抵抗性であるため，G-CSFを併用して短い治療間隔で強力な化学療法を繰り返す．また，しばしば中枢神経系に再発するため予防的に髄注を併用する．慢性型やくすぶり型ATLの治療法は，急性転化するまではwatchful waiting(WW：無治療または皮膚病変などへの局所療法のみで観察)が原則とされるがその長期予後は良好ではない．allo-HSCTは，有害反応は強いが宿主片対ATL効果により長期生存が期待できるので，ドナー，移植の前処置法など症例の選択規準は確立していないが，検討されるべき治療法である[7]．合併症対策としては，高Ca血症の治療と日和見感染症の予防/治療が重要である．

ATLに対する治療法の開発は，これまで主に日本で行われてきた．1970年代から，JCOG-LSGではATLを含むアグレッシブ非ホジキンリンパ腫(NHL)に対し継続的な臨床試験と調査が行われ，以下の知見が得られている[8]．

(1) 他のアグレッシブリンパ腫と同じ治療法によると，いわゆる第1世代，第2世代のいずれの化学療法でも，完全寛解率と全生存割合(OS)でB細胞リンパ腫，ATL以外のT細胞リンパ腫に劣ること(JCOG7801，8101，9701)．そしてATLとの診断が最も予後不良な因子であったこと(JCOG8701)．

(2) 1991年には，ATLの全国調査によるその多様な臨床病態と予後因子の解析結果に基づいて，病型分類を提唱し，その病型分類に基づき，急性型，リンパ腫型，そして予後不良因子(LDH，BUN，Albのいずれかが異常値)をもつ慢性型を対象に，ATLのみに対する臨床試験を以降継続的に実施してきたこと(JCOG9109，9303，9801，0907)．

(3) 1990年代に有望であったプリンアナログの新薬を組み込んでもその予後は改善しなかったこと(JCOG9109)．

(4) NHLの標準治療であるCHOPの4剤に，G-CSFと赤血球・血小板輸血を併用することにより治療強度を高め，ラニムスチン，ビンデ

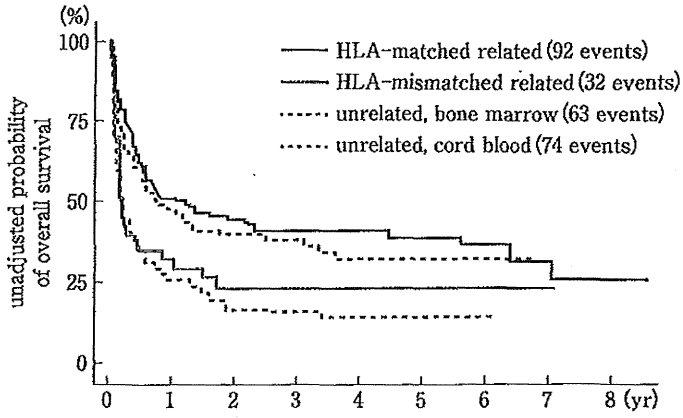


図3 高悪性度ATL 386例に対する同種造血幹細胞移植療法の成績
(文献[9]より改変)

シン，カルボプラチン，エトポシドを組み入れたVCAP-AMP-VECP(mLSG15)療法が，同じくG-CSFを併用しCHOPを3週に1回から2週に1回と治療強度を高めたCHOP-14に完全寛解率と3年OSで上回ったことにより，ATLに対して化学療法を行う場合の標準治療が一応確立したが，VCAP-AMP-VECP療法によるOSでも23％と，他の造血器腫瘍よりも不良であることから，新規治療法の開発が急務であること(JCOG9303，9801)[9].

現在進行中のJCOG0907試験は，本疾患に対して有望なことが次段のように示されつつあるallo-HSCTが，その高いリスクに見合う治療法であるか否かを検証するために，登録された55歳以下の初発アグレッシブATL患者のすべてを対象として，導入化学療法を開始した後，ドナーが確保された場合に骨髄破壊的な前処置法を用いたallo-HSCTを施行する一連の治療の有効性と安全性を，ヒストリカルコントロールである化学療法と比較する非ランダム化の検証的第2相試験である.

現在allo-HSCTは，アグレッシブATLに高率に治癒をもたらす唯一の治療法である(図3)[9]. allo-HSCTでは，移植前処置の強度，ドナー，幹細胞のソースなどにバリエーションがある．特にATLは比較的高齢者に多いことからその工夫が重要となる．厚生労働省がん臨床研究班の岡村班，鵜池班では継続的に，比較的高齢者のアグレッシブATLに対する骨髄非破壊的allo-HSCT(NST)のfeasibility studyをウイルス学的なcorrelative studyとともに行ってきた．その初期の試験結果から，NSTが比較的安全に高齢者ATLにできること，移植片対宿主病(GVHD)を伴うと再発が少ないこと，移植後には細胞傷害性Tリンパ球(CTL)活性が出現し，ウイルス量が減じることを報告してきた[10]．現在は臍帯血を用いた第2相試験が進行中である．一方日本の日本造血細胞移植学会データセンターでの継続的な後方視的解析では，ATLに対するallo-HSCTでは比較的軽いGVHDを伴うと再発が少なく，長期生存が得られやすいこと，NSTが比較的高齢者に長期生存をもたらしていることが報告されてきた.

インドレント(くすぶり型，予後不良因子をもたない慢性型)ATLは，無治療でも数年以上病状が悪化しない場合があることと毒性の軽微な標準治療がないことから，急性転化(アグレッシブATLになること)するまではWWが標準治療とされてきた[7]．しかしその長期予後は同様にWWされるB細胞性慢性リンパ性白血病などに比べて不良であった[11]．未治療のインドレントATL患者を対象としては，欧米ではリンパ腫型以外のATLに対する標準治療の一つとみなされているが日本では保険適用がないインターフェロンαとジドブジンの併用療法(IFN/AZT療法)が，標準治療であるWWよりも有用

であるか否かを検証するために先進医療B評価制度を用いたランダム化第3相試験が開始された(JCOG1111)[12]. 本試験ではATLに対し, 日本では保険適用のないIFNとAZTを先進医療B評価制度による臨床試験で用い, その有用性が検証されれば両剤の保険適用拡大を目指している.

3. ATLを含むT細胞リンパ腫に対する新薬開発の現状と課題

ATLを含むT細胞リンパ腫に対する抗体医薬ほかの新薬の開発が最近進んでいる. 1990年代に開発されたマウス/ヒトキメラ型抗CD20抗体のrituximabはB細胞腫瘍の治療法を一変させた. CC chemokine receptor 4(CCR4)は, 正常組織において, Th2/制御性CD4陽性T細胞に選択的に発現することが知られており, 喘息, アトピー性皮膚炎などのアレルギー性疾患の分子標的として注目されている. 一方T細胞腫瘍においては, ATLの90%以上と末梢性Tリンパ腫(PTCL)非特定型の約30%での発現が報告され, かつCCR4陽性のATL/PTCLは陰性例と比べて皮膚などへの臓器浸潤が強く, また予後不良であった. 糖鎖のフコースを除くことにより抗体依存性細胞傷害活性を高めた抗CCR4ヒト化mogamulizumab(MoAb)が日本で開発され, CCR4陽性の再発T細胞腫瘍を対象に第1相試験が行われた[13]. 再発高悪性度ATL 13例, その他のPTCL 3例を対象に増量が検討され, リンパ球減少と急性輸注反応を主とした毒性は許容範囲であり, 予定していた最大投与量が最大耐用量となった. 奏効割合は31%(完全奏効(CR) 2例, 部分奏効(PR) 2例)と有望であり, 特に末梢血病変によく奏効した. この有望な成績を受けて, mogamulizumabの至適用量とみなされた1.0mg/kgによる再発高悪性度ATLに対する第2相試験が開始され登録は速やかに終了した[14]. 26例での奏効割合は50%(CR 8例, PR 5例)と有望であり, 皮疹などの重篤な有害事象は対処可能であった[13]. この結果, 本剤は再発難治のATLに対して2012年6月から保険適用となった. 再発難治のPTCL/CTCLに対する単剤の第2相試験と初発高悪性度ATLに対する化学療法との併用療法の第2相試験が最近終了し, いずれも有望な成績が学会発表された.

そのほかに日本でATLに対して開発・検討中の新規薬剤としては, 作用機序は多様とされるが骨髄腫, 骨髄異形成症候群ほかで有用性が示されたimmunomoduratory drugのlenalidomide, プロテアゾーム阻害剤のbortezomib, 抗CD30抗体と抗チューブリン薬の複合体であるSGN35, 葉酸拮抗薬のpralatrexate, Tリンパ球で重要なプリン・サルベージ酵素であるpurine nucleoside phosphorylaseの阻害剤, 更には幾つかの免疫療法などがある.

おわりに
—ATL治療の今後の展望—

ATLを含む難治性のT細胞腫瘍に対する治療法の開発には, 基礎・橋渡し研究, そして引き続いての臨床試験が重要である. 極めて難治性であるが多様な病態をとるATLに対する治療戦略としては, WWからallo-HSCTまで幅広い. 予後予測と治療法の選択には臨床病型分類が有用であるが, 今後は予後予測に有用な分子マーカー, 更には初期治療後の残存病変の評価を組み合わせることにより, 多様なATLに対する層別化した標準治療法の開発が望まれている. このためにはATLに対して新たに開発された薬剤を組み入れた集学的治療法について, 検証的な医師主導の臨床試験が重要となる. またATL患者の高齢化が進むなか, 有害反応の少ない新規治療法の開発も求められている.

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＜Special Article＞ 日本から発信されたリンパ腫治療のエビデンス

塚崎邦弘*

要旨

- JCOG リンパ腫グループ(JCOG-LSG)による 1970 年代からの継続的な臨床試験は，日本におけるアグレッシブ非 Hodgkin リンパ腫，Hodgkin リンパ腫，成人 T 細胞白血病・リンパ腫などのリンパ系腫瘍の臨床病理学的特徴の解明とその標準治療の開発に寄与してきた．
- 2000 年以降は，WHO 分類の大改訂によって NK/T 細胞リンパ腫や低悪性度 B リンパ腫に対する臨床試験を行い，その結果は標準治療の確立に寄与することが国際的にも評価されてきた．
- 現在は 5 つの試験を登録中であり，これまでの試験結果の長期フォロー解析と併合解析も行っている．

JCOG リンパ腫グループとは

日本腫瘍臨床研究グループ(Japan Clinical Oncology Group：JCOG)のリンパ腫グループ(LSG)は，1978 年に 5 施設で始まり，現在 47 施設が参加している[1]．JCOG は多施設共同の臨床研究グループであり，LSG を含む 16 のグループからなり，主に市販後の薬剤や放射線治療，手術を組み合わせた集学的治療により，各種癌のガイドラインを書き換えるような新たな標準治療を生み出すことをミッションとしている[2]．JCOG-LSG はこれまでに 10 のランダム化試験を含む 30 以上の臨床試験を，非 Hodgkin リンパ腫(NHL)，成人 T 細胞白血病・リンパ腫(ATL)，リンパ芽球性リンパ腫/急性リンパ性白血病(LBL/ALL)，Hodgkin リンパ腫(HL)，多発性骨髄腫，NK/T-NHL，低悪性度 B-NHL，マントル細胞リンパ腫(MCL)とびまん性大細胞型 B 細胞リンパ腫(DLBCL)を対象に，継続的に行ってきた(Fig. 1)[1]．

LSG の最初の多施設共同臨床試験は，NHL を対象に CHOP 療法の 4 剤(cyclophosphamide, doxorubicin, vincristine, prednisolone)を減量して用いた VEPA 療法の第 II 相試験(JCOG7801)であった[3]．1970～1980 年代の試験では，当時明らかとなりつつあった T/B 細胞表面形質と HTLV-1 の疫学的解析を並行して行い，LBL と ATL を含む末梢性 T 細胞リンパ腫が予後不良であることを明らかにし，その後の個別化治療につなげた

キーワード：多施設共同臨床試験，日本臨床腫瘍研究グループ(JCOG)リンパ腫治療，エビデンス．

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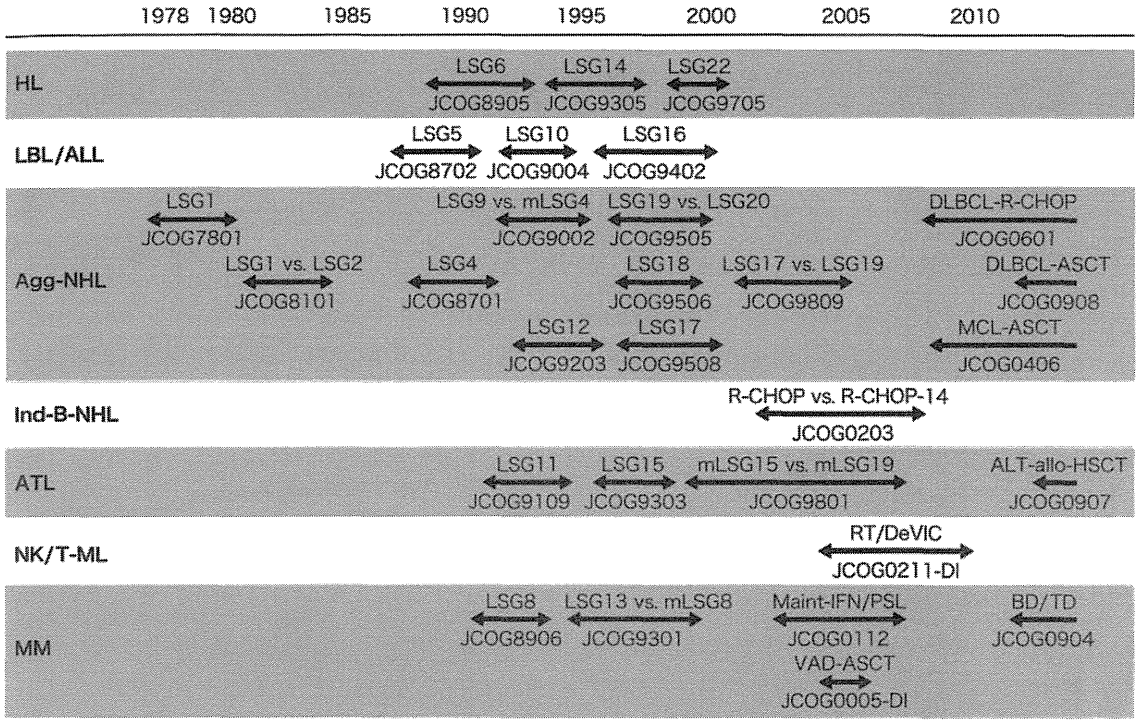

Fig. 1. JCOG-LSG によるリンパ系腫瘍に対する継続的な臨床試験

Agg-NHL：アグレッシブ非 Hodgkin リンパ腫，Ind-B-NHL：インドレント B 細胞リンパ腫，NK/T-ML：NK/T 細胞リンパ腫，MM：多発性骨髄腫．［文献 1）より引用，改変］

(JCOG7801, 8101, 8701)．また，ATL の全国調査によるその多様な臨床病態と予後因子の解析結果に基づいて病型分類を提唱し，その後の ATL 層別化治療につなげた(JCOG9109, 9303)．さらには高悪性度 ATL に対する第Ⅲ相比較試験によって標準的な化学療法を確立した(JCOG9801)[4]．

一方，日本では，欧米と比較してまれな HL に対しては，催吐作用と血管痛が強いため dacarbazine の量を減じた ABVd 療法(doxorubicin＋vinblastine＋bleomycin＋dacarbazine)が欧米の ABVD 療法の成績に遜色なく，わが国の標準治療となり，これが 2 課長通知に基づく dacarbazine の HL に対する保険適用認可に貢献した(JCOG8005, 9305)[5,6]．

アグレッシブ NHL に対して第二，第三世代の化学療法が予後の改善を示さないことが 1990 年代に欧米の臨床試験グループおよび LSG から示されたことにより，依然 CHOP が標準療法とされた(JCOG9002)[7,8]．同時期に，DLBCL を主としたアグレッシブ NHL の予後予測と層別化に国際予後指標(International Prognostic Index：IPI)が有用であることが示されてからは，国内外の臨床試験では当時併用できるようになった G-CSF と自家造血幹細胞移植(ASCT)による治療強度のアップによる予後の改善を期待した[9]．しかし，進行期アグレッシブ NHL に対する JCOG9809 試験では，CHOP-14 群の無増悪生存割合(PFS)が CHOP 群を上回らず[10]，ドイツからの同様の試験結果と異なったことから，治療間隔を短縮する dose-dense 化学療法の評価に一石を投じた．本稿では 2000 年以降の JCOG-LSG でのリンパ腫に対する臨床試験について，これまでの成果と現状を紹介する．

なお，ここに紹介する成果は，JCOG-LSG 参加

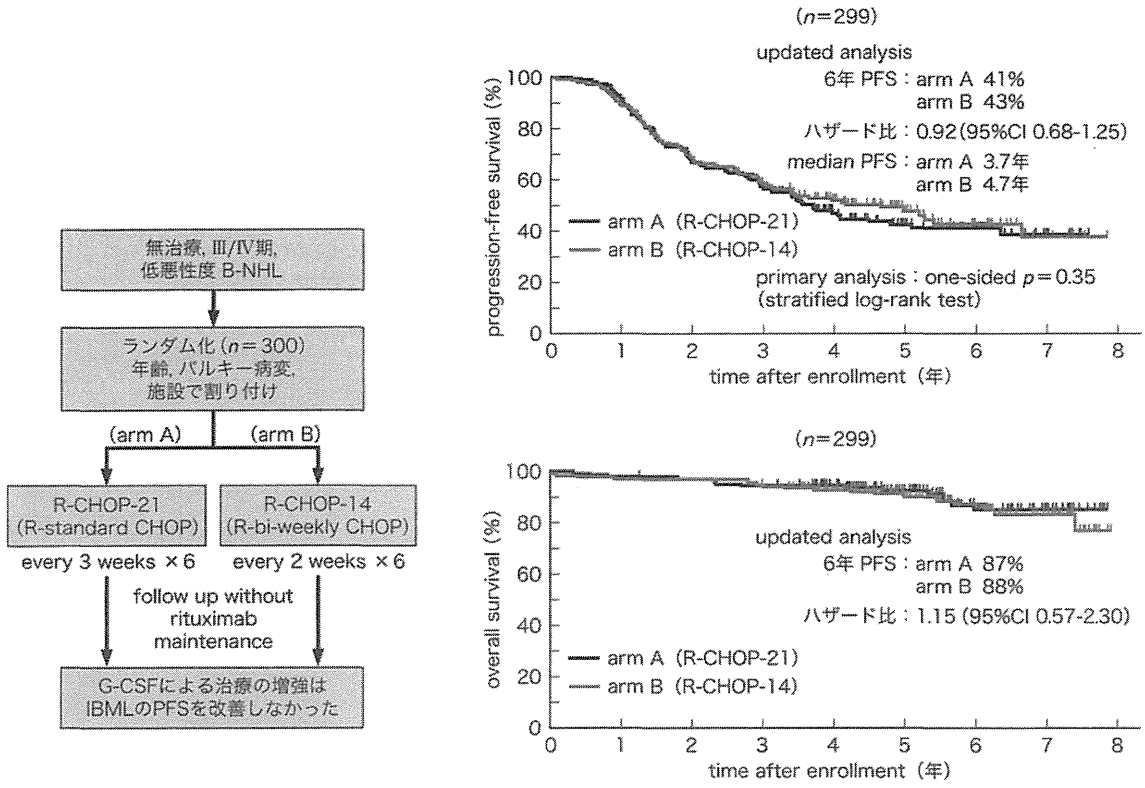

Fig. 2.　JCOG0203

未治療進行期 IBML に対する抗 CD20 抗体療法＋化学療法（rituximab＋CHOP−21 vs. rituximab＋CHOP−14）のランダム化比較第Ⅱ/Ⅲ相試験．

［文献 11）より引用，改変］

施設の医療スタッフ，患者さんの協力に加えて，多施設共同研究グループである JCOG のデータセンターによるデータマネジメントと統計学的検討，15 グループからのピアレビューによるプロトコール・効果・安全性の評価，専門委員会による病理・放射線診断・放射線治療の評価に基づいており，関係各位に深謝したい．

濾胞性リンパ腫を主とした低悪性度 B 細胞リンパ腫●

それまで欧米に比べ日本では少ないとされてきた濾胞性リンパ腫を主とした低悪性度 B リンパ腫（IBML）が日本で増加傾向にあったこと，2001 年に IBML を含む造血器腫瘍の WHO 分類の大改訂があったこと，抗 CD20 抗体の rituximab が日本では DLBCL に先んじて IBML の初発例に適用となったことから，2003 年からこのタイプのリンパ腫に対してのはじめての臨床試験を第Ⅱ/Ⅲ相比較試験として行った（JCOG0203）[11]．当時，IBML に対しての標準治療を確立するための欧米の臨床研究では rituximab の有無の比較でその併用の有用性が示されていたので，本試験では rituximab 併用の相手の化学療法についてランダム化比較試験を行うこととし，当時標準治療の一つとみなされていた R-CHOP 療法（CHOP＋rituximab）とそれに G-CSF を併用することにより治療間隔を狭め，かつ ADCC 活性の増強を図った R-CHOP-14 を比較検討した．本試験では当初の予定よりも登録ペースが速く，5 年間で 300 例を登録できた．第Ⅱ相部分の中間解析では両群の

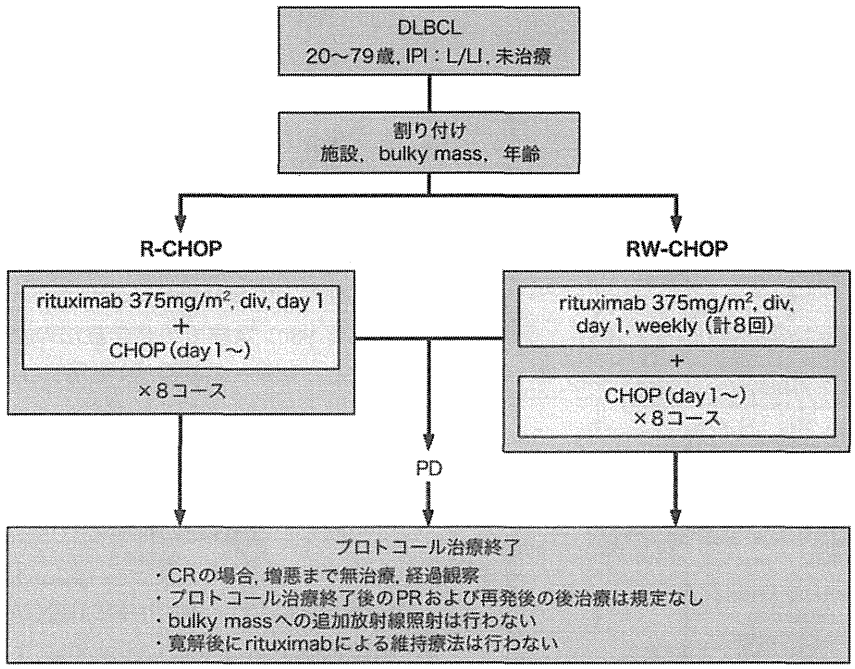

Fig. 3. JCOG0601
未治療の CD20 陽性 DLBCL に対する R-CHOP 療法における rituximab の投与スケジュールの検討を目的としたランダム化第Ⅱ/Ⅲ相試験.
(http://www.jcog.jp/basic/org/group/lsg.html)

高い安全性と奏効割合を確認できた．最終解析では，R-CHOP-14 と R-CHOP-21 ともに完全寛解(CR)割合は 76% と 78% と高く，主たる評価項目である PFS は Fig. 2 に示すように 6 年で 88% と 87% とともに高く，差はなく，G-CSF の併用効果は認めなかった[11]．日本人 IBML の多数例での解析は JCOG0203 がはじめてであり，現在はこの登録患者をフォローすることにより，本疾患群の長期予後を明らかにする二次研究が進行中である．

びまん性大細胞型 B 細胞リンパ腫●

前述したアグレッシブ NHL に対する JCOG9809 試験で CHOP 療法に CHOP-14 療法が勝らなかったこと，2002 年に論文化された GELA の試験で DLBCL に対して CHOP 療法に比べて R-CHOP 療法が全生存割合(OS)を改善したことから[12]，JCOG では標準治療の R-CHOP 療法に勝る治療法を開発するために，それぞれ IPI 低リスク(L/LI)群と高リスク(HI/H)群を対象に 2006 年と 2009 年から 2 つの試験を開始した．前者は未治療 CD20 陽性 DLBCL に対する R-CHOP 療法における rituximab の至適投与法を確立するためのランダム化第Ⅱ/Ⅲ相試験(JCOG0601)であり，週 1 回の rituximab×8 回と 3 週ごとの CHOP を併用する試験治療の RW-CHOP が，rituximab の血中濃度を早期に高めることにより標準治療の R-CHOP に比べて PFS の改善をもたらすかを検証する(Fig. 3)．また後者は，未治療の CD20 陽性高リスク DLBCL を対象として，ASCT を伴う大量化学療法(LEED 療法(melphalan + cyclophosphamide + etoposide + dexamethasone))に先立って行う rituximab 併用導入化学療法として，CHOP-14 療法と CHOP-14/

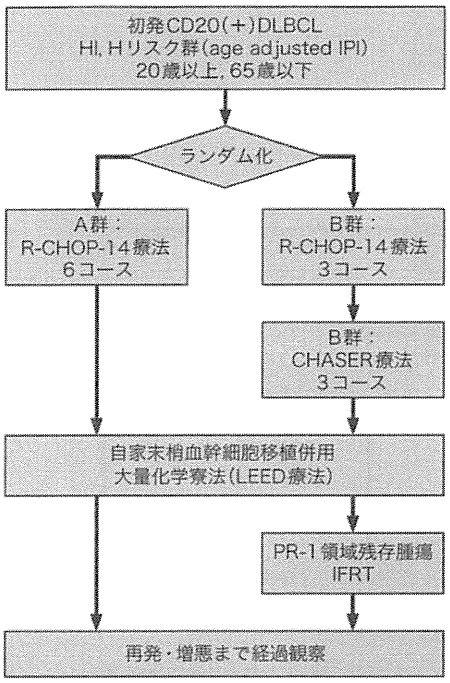

Fig. 4　JCOG0908

高リスク DLBCL に対する導入化学療法(R-CHOP-14 療法または R-CHOP-14/CHASER 療法)と大量化学療法(LEED)の有用性に関するランダム化第Ⅱ相試験.

IFRT：involved field radiotherapy.

(http://www.jcog.jp/basic/org/group/lsg.html)

CHASER 療法のいずれが有望かを主たる評価項目の PFS で判断するランダム化第Ⅱ相試験(JCOG0908)である(Fig. 4).

成人 T 細胞白血病・リンパ腫●

前述した JCOG9801 試験で CHOP-14 と比べて有意に高い CR 割合と marginal に高い OS を示した VCAP(vincristine＋cyclophosphamide＋doxorubicin＋prednisolone)-AMP(doxorubicin＋ranimustine＋prednisolone)-VECP(vincristine＋etoposide＋carboplatin＋prednisolone)療法を，よりよい標準治療を開発するためのベースとなる治療とみなして，アグレッシブ ATL に対して移植片対 ATL 効果により治癒を含む高い長期生存割合が期待されている骨髄破壊的な同種造血幹細胞移植(allo-HSCT)の試験(JCOG0907)を 2009 年から実施している(Fig. 5)．本研究は，ATL に対する allo-HSCT がその高いリスクに見合う治療法であるか否かを検証するために，20 歳以上 55 歳以下の ATL 患者を対象として，導入化学療法を開始した後，ドナーが確保された場合に骨髄破壊的な前処置法を用いた allo-HSCT を施行する一連の治療の有効性と安全性をヒストリカル・コントロールである 9801 試験での化学療法の全生存割合と比較する．ドナーを必要とする allo-HSCT の特殊な事情からランダム化比較試験はむずかしいことから，本試験は検証的第Ⅱ相試験と位置づけた．

また，未治療の indolent ATL 患者を対象として，欧米では ATL に対する標準治療の一つとみなされているインターフェロン α(IFN-α)と zidovudine(AZT)の併用療法(IFN/AZT 療法)が，標準治療である watchful waiting よりも有用であるか否かを検証するため，PFS を主たる評価項目としたランダム化第Ⅲ相試験を計画している(JCOG1111)．本試験では ATL に日本では保険適用のない IFN と AZT を高度医療評価制度による臨床試験で用い，その有用性が検証されれば両剤の保険適用の拡大を目指している．

限局期鼻 NK/T 細胞リンパ腫●

JCOG-LSG で 1990 年代に継続的に行ってきた 6 つの臨床試験の併合解析結果では，B 細胞リンパ腫よりも ATL を除く T 細胞リンパ腫の予後は不良であり，その中でも節外性 NK/T 細胞リンパ腫は予後不良であった[13]．

欧米に比べて東南アジアに多いが，日本ではその中間の頻度とされる未治療限局期鼻 NK/T 細胞リンパ腫に対して，2002 年から放射線治療と DeVIC 療法(carboplatin＋ifosfamide＋etoposide＋dexamethasone)との同時併用療法の第Ⅰ/Ⅱ相試験(JCOG0211-DI)を実施した[14]．50 Gy 照射との併用 DeVIC 療法の第Ⅰ相での検討では，10 例による至適用量は 2/3 量であり，全登録 33 例での CR 割合は 77%，2 年 OS は 78% であった(Fig.

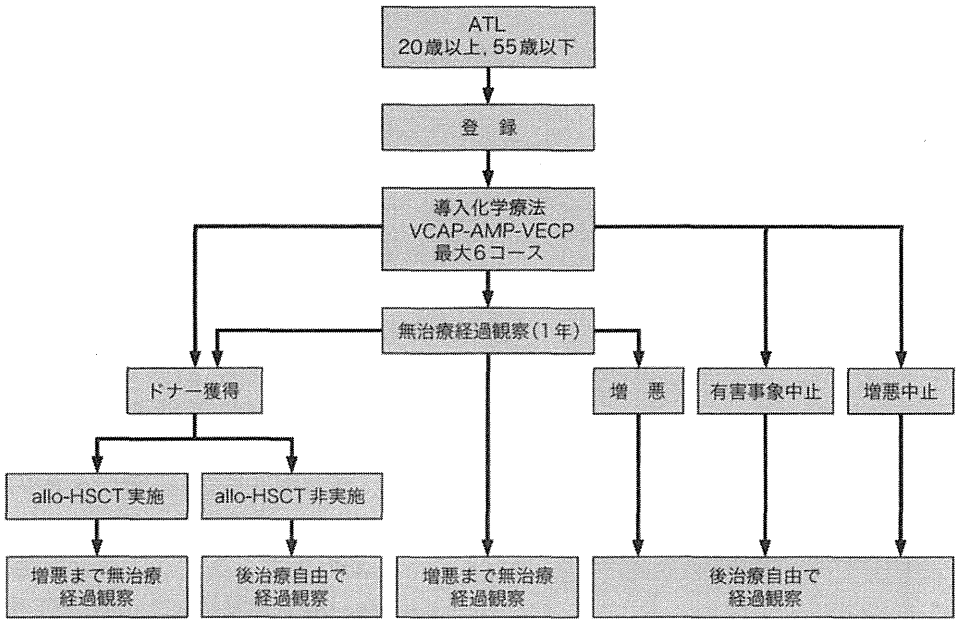

Fig. 5. JCOG0907
ATL に対する骨髄破壊的前処置法を用いた allo-HSCT を組み込んだ治療法に関する第Ⅱ相試験.
(http://www.jcog.jp/basic/org/group/lsg.html)

6)．三度の非血液毒性では照射に関連する口内炎が 30% と最多であったが忍容でき，治療関連死は認めなかった．ヒストリカル・コントロールの照射単独での 2 年 OS の 45% よりも上回っていたことから，放射線治療と 2/3 量 DeVIC 療法との同時併用療法は，希少疾患のため第Ⅲ相比較試験の実施が困難な限局期鼻 NK/T 細胞リンパ腫に対する標準治療と位置づけられる．二次研究として，現在 JCOG0211-DI 登録症例を長期フォローすることにより，晩発性の有害事象を含めた長期予後を明らかにする研究と，比較的遠隔再発が多かったことから腫瘍生検組織と骨髄組織を用いた免疫組織化学的検討を行い，その結果を治療前患者背景，治療反応性および予後と比較し，探索的に検討する研究を行っている．

おわりに●

日本から発信されたリンパ腫治療のエビデンスとして，2000 年以降の JCOG-LSG 臨床試験結果と進行中の試験を疾患単位ごとに紹介した．このほか JCOG-LSG では，DLBCL と IBML の中間の予後をとり難治性であるマントル細胞リンパ腫に対する rituximab と自己末梢血幹細胞移植併用の大量化学療法の第Ⅱ相試験(JCOG0406)，骨髄腫に対する継続的な試験も実施している．最近の試験では付随研究として試料を用いた治療効果予測の検討を実施しているほか，予後予測と層別化治療に有望視されている interim PET については，HL に対する次期臨床試験で中央診断を含めて検討中である．

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