malignancies, autologous/allogeneic (auto/allo)-hematopoietic stem cell transplantation (HSCT) with the prophylactic use of granulocyte colony-stimulating factor (G-CSF), and thalidomide and its derivatives and proteasome inhibitor for multiple myeloma (MM) (6,7).

Along with these advances in research for lymphoid malignancies, JCOG-LSG, which was initiated in 1978, has conducted more than 30 clinical trials including 10 randomized trials to establish new standard therapies for lymphoid malignancies (Tables 1–7 and Fig. 1) (8–10). In this article, we summarize the development of JCOG-LSG with the results of clinical trials.

HISTORY OF JCOG-LSG

Conducting clinical trials for the development of standard therapies requires investigators, a coordinating center and committees under the support of grant providers (8–10). Now, LSG, as in the case of other cancer study groups in JCOG, is conducting trials under the organization of JCOG. At first in 1978, following the success of multi-institutional clinical trials of oncology in the USA, a directed research project entitled 'A Study on Multidisciplinary Treatment for Solid Cancer' was started. Several disease committees including LSG have been supported since then by Grants-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare (MHLW) in Japan. LSG was initiated in 1978 with only five institutions chaired by Masanori Shimoyama, MD, and included the T- and B-cell Malignancy Study Group as a subgroup to conduct epidemiological studies of ATL. It then grew to 17 institutions during 1980–84 to perform virological studies on ATL, resulting in the discovery of an etiological retrovirus called ATL virus by Yorio Hinuma, MD, in 1981. Meanwhile, LSG has conducted clinical trials for non-Hodgkin's lymphoma (NHL) and later formed the Lymphoma Clinico-Pathological Panel to evaluate the reproducibility agreement rates of the pathological diagnosis of NHL. Then, the Autologous Bone Marrow Transplantation Study Group was initiated by Kensei Tobinai, MD, in 1990, which was later integrated into the LSG and the Breast Cancer Study Group in 1999. [LSG now consists of 47 institutions as an active disease committee in JCOG.]

Along with the development of standing committees and a statistical center, the multicenter cooperative oncology group was named the Japan Clinical Oncology Group (JCOG) in 1990. JCOG has now a common Data Center, a Steering Committee and each of 13 cancer study groups including LSG. JCOG-LSG has conducted consecutive studies for

Table 1. Results of the JCOG-LSG trials for advanced aggressive non-Hodgkin's lymphoma (NHL)

Protocol	Regimen	Patients risk category	Phase	No. of patients	%CR and uncertified CR	MST (months)	Survival (%)	Reference
JCOG7801	VEPA	All	II	100	52	NA	NA	11
JCOG8101		All	III	163				12
	VEPA			81	52	17	27 (4 years)	
	VEPA-M			82	62	24	37 (4 years)	
JCOG8701	LSG4	All	II	267	72	39	48 (5 years)	13
JCOG9002		All	III	447	67	NA	56 (5 years)	14
	LSG9			230	70	91	57 (5 years)	
	modified LSG4			217	65	78	55 (5 years)	
JCOG9203	VEPA/FEPP	Elderly	II	45	60	52	42 (5 years)	58
JCOG9505	upfront ASCT	HI/H	R-II	70	56	12	42 (4 years)	18
	CHOP-14			35	60	NA	42 (4 years)	
	DE-CHOP			35	51	NA	42 (4 years)	
JCOG9506		HI/H	II	43	NA	NA	58 (3 years)	NA
JCOG9508	CHOP	L/LI	II	213	NA	NA	74 (4 years)	17
JCOG9809		All	III	323[a]			74 (2 years)	19, 20
	CHPO-14			162	67	NR	55 (8 years)	
	CHOP			161	62	NR	56 (8 years)	

VEPA consisting of vincristine (VCR), cyclophosphamide (CPA), prednisone (PSL) and doxorubicin (DOX); VEPA-M consisting of VEPA + methotrexate (MTX); LSG4 consisting of VEPA-B, M-FEPA and VEPP-B, where VEPA-B consisting of VEPA + bleomycin (BLM), M-FEPA consisting of moderate dose of MTX, vindesine (VDS), CPA, PSL and DOX, and VEPP-B consisting of VCR, CPA, PSL and procarbazin (PCZ); LSG9 consisting of dose-intensified mLSG4; DE-CHOP: dose-escalated CHOP; CR, complete response; MST, median survival time; NA, not applicable; NR, not reached, R-II, randomized Phase II study; ASCT, autologous stem cell transplantation.
[a]Number of enrolled patients until the early termination.

Table 2. Results of the JCOG trials for adult T-cell leukemia–lymphoma

Protocol	Regimen	Phase	No. of patients	%CR	MST (months)	Survival (%)	Reference
JCOG7801	VEPA	II	18	17	5	0 (3 years)	11
JCOG8101		III	54	28	8	8.3 (4 years)	12
	VEPA		24	17	NA	NA	
	VEPA-M		30	37	NA	NA	
JCOG8701	LSG4	II	42	43	8	12 (5 years)	13
JCOG9109	LSG11	II	60	28	7	16 (2 years)	31
JCOG9303	LSG15	II	93	36	13	31 (2 years)	32
JCOG9801		III	118				33
	mLSG15		57	40	13	24 (3 years)	
	CHOP-14		61	25	11	13 (3 years)	

For abbreviations, see Table 1. LSG 11 consists of 2′-deoxycoformycin, VCR, ETP, PSL and DOX; LSG15 consists of VCAP (VCR, CPA, PSL and DOX), AMP [DOX, raimustine (MCNU), VECP [VDS, ETP, carboplatin (CBDCA) and PSL], intrathecal MTX + PSL, with each intensified by the prophylactic use of G-CSF (granulocyte colony-stimulating factor); mLSG15 is a modified LSG15.

Table 3. Results of the JCOG trials for lymphoblastic lymphoma/acute lymphoblastic leukemia

Protocol	Regimen	Phase	No. of patients	%CR	PFS (%)	MST (months)	Survival (%)	Reference
JCOG8702	LSG 5	II	46	78	NA	14	15 (7 years)	38
JCOG9004	LSG10	II	143	83	26 (5 years)	26	32 (7 years)	39
JCOG9402	LSG16	II	108	81	28 (5 years)	21	28 (7 years)	40

For abbreviations, see Tables 1 and 2. PFS, progression-free survival; LSG5 consists of VEPA-L [VEPA with L-asparaginase (L-ASP) and intrathecal (IT) MTX/PSL] and M-VEPA (moderate-dose methotrexate plus VEPA); LSG10 consists of induction by LSG5/consolidation by DCMP (DOX, AraC, VDS, PSL, IT-MTX/PSL)/MEVP (mitoxantron, ETP, VCR, PSL, IT-MTX/PSL)/maintenance by 6-mercaptopurine (6-MP)/MTX, with allowing HSCT; LSG16 consists of induction by VEPA-L/consolidation by DCMP and CCMOL (CPA, AraC, 6-MP, VCR, L-ASP with IT-MTX/PSL)/intensified maintenance with allowing HSCT.

Table 4. Results of the JCOG trials for advanced Hodgkin's lymphoma

Protocol	Regimen	Phase	No. of patients	%CR	PFS (%)	Survival (%)	Reference
JCOG8905	C-MOPP/ABVd	II	79	84	73 (4 years)	85 (5 years)	41
JCOG9305	ABVd	II	128	81	78 (5 years)	91 (5 years)	42
JCOG9705	ABV + R	II	72[a]	72	49 (2 years)	92 (2 years)	44

For abbreviations, see Tables 1–3. C-MOPP consists of CPA, VLB, PCZ and PDN; ABVd consists of DOX, BLM, VLB and dacarbazine (DTIC); ABV + R consists of DOX, BLM, VLB with radiation.
[a]No. of enrolled patients with eligibility until the early termination.

lymphoid malignancies since 1978 with the help of the Central Pathology Review, the Radiation Therapy Quality Assurance and the Central CT Review Committees.

The research on treatments for lymphoid malignancies by JCOG-LSG is now supported by four grants for the principal investigators of the LSG studies by MHLW and Grants-in-Aid for Cancer Research (23A-17). JCOG-LSG has conducted more than 30 clinical trials including 10 randomized trials for several entities of lymphoid malignancies, meta-analyses of them, and correlative epidemiological and pathological studies on HTLV-1 and T/B-cell phenotype, respectively, providing several standard treatments, classifications and prognostic indexes for lymphoid malignancies as shown in the following sections.

Table 5. Results of the JCOG trials for advanced multiple myeloma

Protocol	Regimen	Phase	No. of patients	%RR (no)	Median PFS	MST (months)	Survival (%)	Reference
JCOG8906	COP/MP	II	69	51	13	39	51/27 (3/5 years)	48
JCOG9301		III	210					49
	MCNU-COP/MP		107	56	23	50	38 (5 years)	
	mCOP/MP		103	44	16	44	40 (5 years)	
JCOG0005-DI	VAD and up-front auto-HSCT	II	16[a]	NA	NA	NA	NA	NA
JCOG0112	MP/VAD with IFN + PSL versus PSL	III	34[a]					50
	VAD		16	44	NA	NA	NA	
	MP		17	47	NA	NA	NA	

For abbreviations, see Tables 1–4. DI, Data Center independent; IFN, interferon-α; COP consists of CPA, VCR and PSL; MP consists of melphalan and PSL; mCOP/MP is a modified COP/MP; VAD consists of VCR, DOX and dexamethasone.
[a]No. of enrolled patients until the early termination.

Table 6. Results of the JCOG trials for indolent B-cell lymphomas and localized nasal natural killer/T-cell lymphoma

Protocol	Regimen	Diseases	Phase	No. of patients	%CR/CRu (no)	PFS (%)	Survival (%)	Reference
JCOG0203		Indolent B	III	300				52
	CHOP-14			151	76	43 (6 years)	88 (6 years)	
	CHOP-21			149	78	41 (6 years)	87 (6 years)	
JCOG0211-DI	DEVIC/50 Gy	Nasal NK/T	I/II	33	77 (20/26)	67 (2 years)	78 (2 years)	56

For abbreviations, see Tables 1–5. DEVIC consists of DEX, ETP, ifosfamide (IFM) and CBDCA.

Table 7. Summaries of the JCOG-LSG correlative studies on trials for malignant lymphomas

Protocol	Trials	Disease	No. of patients	Reference
JCOG0108-A	9305, 0705	Hodgkin	167	45
JCOG0108-A	9002, 9203, 9505, 9506, 9508, 9809	NHL	1141	55
		DLBCL		NA
		T/NK	136	55
JCOG0103-A		NHL	499	59

For abbreviations, see Tables 1–6. NHL, non-Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; T/NK, peripheral T and NK-cell lymphomas.

CONSECUTIVE AND ONGOING TRIALS FOR MAJOR LYMPHOID MALIGNANCIES BY JCOG-LSG

Advanced-stage, Aggressive NHL

Since 1978, chemotherapy trials have been consecutively conducted for patients with advanced-stage, aggressive NHL in JCOG-LSG (Table 1 and Fig. 1). After the completion of JCOG7801, a Phase II study of VEPA therapy (vincristine, cyclophosphamide, prednisone and doxorubicin), with promising results, JCOG-LSG started in 1981 a randomized Phase III trial (JCOG8101) to evaluate VEPA versus VEPA-M [VEPA plus methotrexate (MTX)] for advanced-stage NHL (11,12). The difference in survival between the two arms was not significant; however, unique pretreatment variables predictive for efficacy were found. Three factors, leukemic change, poor performance status (PS) and T-cell phenotype, were negatively associated with both the complete remission rate (%CR) and overall survival (OS). In addition, ATL was found to have a much poorer in prognosis than non-ATL peripheral T-cell lymphoma (26).

In 1987, JCOG-LSG initiated a Phase II study (JCOG8701) of a multiagent combination chemotherapy (LSG4 protocol) for advanced aggressive NHL (10). The LSG4 protocol consisted of three regimens: (i) VEPA-B (VEPA plus bleomycin), (ii) M-FEPA (MTX, vindesine, cyclophosphamide, prednisone and doxorubicin) and (iii) VEPP-B (vincristine, etoposide, procarbazine, prednisone and bleomycin). A central pathology review revealed 84 patients with T-NHL, including 42 with ATL, 151 with B-NHL and 33 with NHL of undetermined lineage

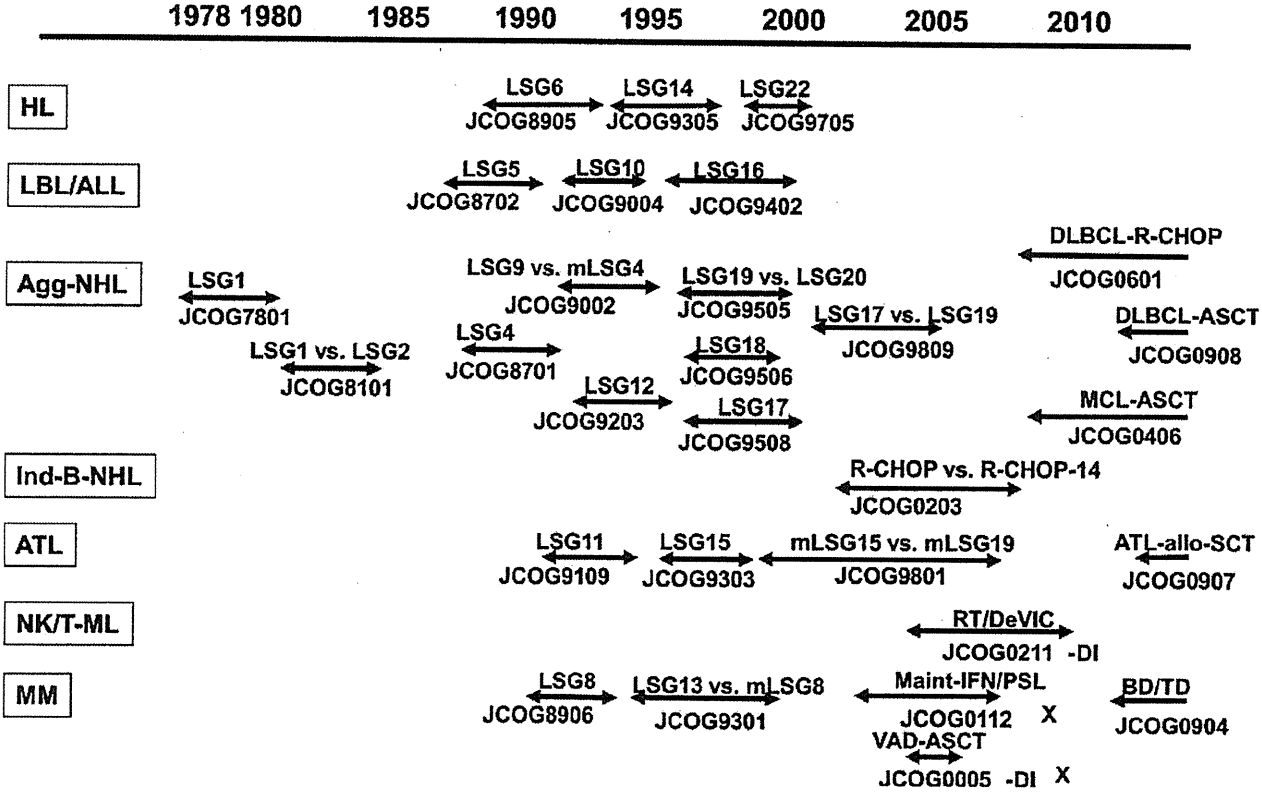

Figure 1. Consecutive studies by JCOG-LSG. HL, Hodgkin's lymphoma; LBL/ALL, lymphoblastic lymphoma/acute lymphoblastic leukemia; Agg-NHL, aggressive non-Hodgkin's lymphoma; Ind-B-NHL, indolent B-NHL, ATL; adult T-cell leukemia–lymphoma; NK/T ML, localized nasal natural killer/T-cell lymphoma; MM, multiple myeloma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma. LSG1, VEPA, consists of vincristine (VCR), cyclophosphamide (CPA), prednisone (PSL) and doxorubicin (DOX); LSG2, VEPA-M, consists of VEPA plus methotrexate (MTX); LSG4 consists of VEPA-B, M-FEPA and VEPP-B, where VEPA-B consists of VEPA plus Bleomycin (BLM), M-FEPA consists of a moderate dose of MTX, vindesine (VDS), CPA, PSL and DOX, and VEPP-B consists of VCR, CPA, PSL and procarbazin (PCZ); LSG5 consists of VEPA-L [VEPA with L-asparaginase (L-ASP) and intrathecal (IT) MTX/PSL] and M-VEPA (moderate-dose methotrexate plus VEPA); LSG6 consists of C-MOPP/ABVd; C-MOPP consists of CPA, VLB, PCZ and PDN; ABVd consists of DOX, BLM, VLB and dacarbazine (DTIC); LSG8 consists of COP/MP; COP consists of CPA, VCR and PSL; MP consists of melphalan and PSL; mLSG8 is a modified LSG8; LSG9 consists of dose-intensified mLSG4; LSG10 consists of induction by LSG5/consolidation by DCMP (DOX, AraC, VDS, PSL, IT-MTX/PSL)/MEVP (mitoxantron, ETP, VCR, PSL, IT-MTX/PSL)/maintenance by 6-mercaptopurine (6-MP)/MTX, with HSCT; LSG11 consists of DCF, VCR, ETP, PSL and DOX; LSG12 consists of VEPA/FEPP, where FEPP consists of vindesine, etoposide, procarbazine and prednisolone; LSG13 consists of raimustine (MCNU)-COP/MP; LSG14 consists of ABVd; LSG15 consists of VCAP (VCR, CPA, PSL, DOX), AMP (DOX, MCNU, PSL), VECP [VDS, ETP, carboplatin (CBDCA), PSL], intrathecal MTX + PLS, with each intensified by the prophylactic use of G-CSF (granulocyte colony-stimulating factor); mLSG15 is a modified LSG15; LSG16 consists of induction by VEPA-L/consolidation by DCMP and CCMOL (CPA, cytarabine, 6-MP, VCR, L-ASP with IT-MTX/PSL)/intensified maintenance with allowing HSCT; LSG17, CHOP, consists of CPA, DOX, VCR and PSL; LSG18 consists of CHOP-14 followed by up-front autologous hematopoietic stem cell transplantation (auto-HSCT); LSG19 consists of CHOP-14; LSG22, ABV + R, consists of DOX, BLM, VLB with radiation; RT/DeVIC in JCOG0005DI consisting of VAD (VCR, DOX and DEX) followed by up-front auto-HSCT; Maint-IFN/PSL in JCOG0112 consisting of MP/VAD induction therapy followed by maintenance therapy with interferon plus PSL versus PSL; R-CHOP and R-CHOP-14 in JCOG0203 consisting of rituximab plus CHOP and rituximab plus CHOP-14, respectively; MCL-ASCT in JCOG0406 consisting of R-high-CHOP followed by CHASER, LEED and auto-HSCT; DLBCL-R-CHOP in JCOG0601 consisting of weekly rituximab plus CHOP versus R-CHOP; BD/TD in JCOG0904 consisting of bortezomib plus dexamethasone versus thalidomide plus dexamethasone; ATL-allo-HSCT in JCOG0907 consisting of mLSG15 followed by allo-HSCT; DLBCL-ASCT in JCOG0908 consists of R-CHOP-14 versus R-CHOP-14 followed by CHASER as induction therapy prior to LEED and auto-HSCT.

(U-NHL). After a median follow-up of 56 months, the estimated overall 5-year OS rate was 48%: 60% in B-NHL, 45% in U-NHL, 35% in PTCL and 12% in ATL (Fig. 2). Unfavorable factors influencing OS that remained independently significant in Cox's analyses were clinical diagnosis of ATL, total number of involved lesions ≥ 4, C-reactive protein-positivity and Eastern Cooperative Oncology Group PS ≥ 2. JCOG8701 led to the following conclusions: (i) T-cell phenotype was an important pretreatment variable for aggressive NHL in Japan, and (ii) LSG4 protocol was effective against B-NHL. Since the clinical diagnosis of ATL was an independent unfavorable factor, ATL patients were excluded from subsequent JCOG trials for aggressive NHL, but LSG has started clinical trials specialized for ATL since then.

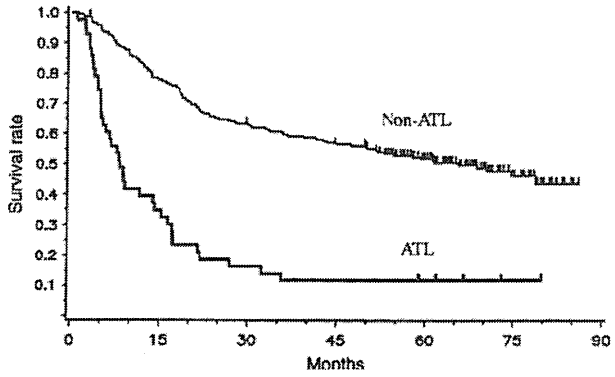

Figure 2. The Kaplan–Meier estimate of overall survival for all patients treated with LSG4 in relation to disease entity. ATL, adult T-cell leukemia–lymphoma.

JCOG9002, a randomized Phase III study, evaluated the dose-intensification strategy for doxorubicin and cyclophosphamide in the third-generation multiagent combination chemotherapy, LSG9 (VEPA-B/FEPP-AB/M-FEPA every 10 weeks; three courses, 28 weeks in total), when compared with second-generation combination chemotherapy, modified LSG4 (mLSG4) (VEPA-B/FEPP-B/M-FEPA every 14 weeks; four courses, 54 weeks in total) (14). Planned dose intensity (DI)/week of DOX and CPA was 1.9- and 1.5-fold higher in LSG9 than in mLSG4, respectively. Median actual DIs of DOX and CPA were 1.6- and 1.2-fold higher in LSG9 than in mLSG4, respectively, with no difference in 5-year OS and the %CR, revealing no survival benefit of the DI strategy.

In 1993, an intergroup US Phase III study revealed that CHOP remained the standard therapy for aggressive NHL when compared with second- and third-generation regimens (15). Also, the international prognostic index (IPI) for patients with aggressive NHL was developed (16). Based on these findings, JCOG-LSG changed the treatment strategy for aggressive NHL from the multiagent chemotherapies to the dose intensification of key agents, and initiated several Phase II studies of regimens based on CHOP for patients divided by IPI risk grouping. Among them, JCOG9508, a Phase II study of standard CHOP every 3 weeks for low and low-intermediate (L/LI)-risk patients with advanced aggressive NHL, revealed that the full dose of CHOP was feasible and effective for Japanese patients as for westerners (17).

JCOG9505, a randomized Phase II study of CHOP every 2 weeks (CHOP-14) and dose-escalated CHOP both supported with the prophylactic use of G-CSF in high-intermediate and high (HI/H)-risk aggressive NHL, revealed that the former was more promising with similar %CR and progression-free survival (PFS) rates, but lower toxicity (18). Following the results of JCOG9505, a randomized Phase III (JCOG9809) study comparing CHOP-14 with CHOP-21 in patients newly diagnosed with advanced-stage aggressive NHL at all IPI risk was conducted (19,20). A planned interim analysis revealed that dose intensification with interval shortening of CHOP did not prolong PFS in advanced, aggressive NHL, resulting in an early stop to the study (19), and long-term follow-up confirmed the results (20). There were no remarkable differences in PFS or OS between the two arms. Secondary malignancies, including myelodysplastic syndrome, were significantly more frequent in the CHOP-14 arm.

Since around 2000, rituximab (R), an anti-CD20 monoclonal antibody, has changed the treatment strategy for all CD20-expressing B-cell neoplasms including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (21). Six to eight courses of rituximab plus CHOP (R-CHOP) every 3 weeks (R-CHOP-21) is now the standard therapy for DLBCL of all risk groups (22). To evaluate the efficacy of DI of rituximab, a randomized Phase II/III study, JCOG0601, is now ongoing comparing the standard with weekly R-CHOP for DLBCL, based on the results of a pharmacokinetic analysis of rituximab monotherapy in a Phase II study for relapsed or refractory aggressive B-NHL (23).

High-dose chemotherapy (HDC) supported with auto-HSCT has been evaluated after induction chemotherapy to improve the prognosis for poor-risk aggressive NHL. However, the results have been controversial in the era before rituximab (24). The US intergroup has conducted a randomized Phase III study evaluating the efficacy of the addition of HDC/auto-SCT after R-CHOP for high-risk DLBCL (25). Considering the next step in the clinical trial for poor-risk DLBCL, JCOG-LSG is now conducting a randomized Phase II study of R-CHOP every 2 weeks (R-CHOP-14) versus R-CHOP-14 followed by CHASER (cyclophosphamide, cytarabine, dexamethasone, etoposide, rituximab) as induction therapy prior to HDC, LEED (melphalan, cyclophosphamide, etoposide, dexamethasone) and auto-HSCT in poor-risk DLBCL (JCOG0908).

Adult T-cell Leukemia–Lymphoma

JCOG-LSG has consecutively studied the treatment of ATL, which was discovered as a new disease entity just before the establishment of LSG. The earlier trials revealed a poor prognosis of ATL when compared with the other aggressive NHL (JCOG7801, 8101, 8701) (11,13,26). Then, a nationwide survey in 854 patients with ATL in Japan revealed that the major prognostic factors were advanced PS, high lactic dehydrogenase (LDH) level, age of 40 years or more, more than three involved lesions and hypercalcemia by multivariate analysis (27). Also, a classification of clinical subtypes into acute, lymphoma, chronic and smoldering types was proposed based on prognostic factors and clinical features of the disease (28). This subtype classification has been reported to be reproducible for predicting prognosis and has been widely applied for treatment decisions. Recently, a treatment strategy based on the clinical subtype classification and prognostic factors was suggested, including a watchful waiting approach, chemotherapy, antiviral therapy,

allo-HSCT and targeted therapies for clinical trials and clinical practice (29).

The disappointing results with conventional chemotherapies in the 1980s and the proposal for a subtype classification of ATL have led to a search for new active agents focusing on aggressive ATL in JCOG-LSG. The first Phase II study of combination chemotherapy with pentostatin (2′-deoxycoformycin, an inhibitor of adenosine deaminase) was conducted exclusively against aggressive ATL, based on the promising results of pentostatin monotherapy for relapsed or refractory ATL patients (30). However, the results were disappointing with a median survival time (MST) of 7 months similar to previous studies by JCOG-LSG (31). The next Phase II trial (JCOG9303) consisting of vincristine, cyclophosphamide, doxorubicin and prednisone (VCAP); doxorubicin, ranimustine and prednisone (AMP); and vindesine, etoposide, carboplatin and prednisone (VECP) intensified with the prophylactic use of G-CSF revealed a promising response rate and MST superior to those obtained by our previous trials, despite considerable hematological toxicity (32). Based on the promising results of JCOG9303, we conducted a Phase III trial comparing modified (m)LSG15 (VCAP–AMP–VECP) with CHOP-14 both supported with G-CSF and intrathecal prophylaxis. The longer survival at 3 years and higher %CR with VCAP–AMP–VECP compared with CHOP-14 suggest that the former is a more effective regimen at the expense of greater toxicity, providing the basis for future investigations in the treatment of ATL (33). However, the MST of 13 months still compares unfavorably to other hematologic malignancies.

Allo-HSCT is now recommended for the treatment of young patients with aggressive ATL (29). To evaluate the promising efficacy of allo-HSCT, possibly associated with a graft-versus-ATL effect, especially in view of a comparison with intensive chemotherapy, a prospective multicenter Phase II study of mLSG15 chemotherapy followed by allo-HSCT, comparing the results with historical control in JCOG9801, has been initiated as JCOG0907.

A combination of interferon-α (IFN) and zidovudine (AZT) was reported as promising for the treatment of ATL in small Phase II trials in 1995 from the USA and Europe (34–36). Recently, in a worldwide retrospective analysis, it was reported that this combination might be effective especially for indolent ATL when compared with watchful waiting (37). A prospective Phase III study evaluating the efficacy of IFN/AZT when compared with watchful waiting for indolent ATL is to be initiated (JCOG PC908) under the highly advanced medical technology assessment system because IFN and AZT are not covered for ATL by the National Health Insurance in Japan.

Lymphoblastic Lymphoma/Acute Lymphoblastic Leukemia

Lymphoblastic lymphoma (LBL)/acute lymphoblastic leukemia (ALL) is a malignancy of immature T/B lymphoblasts and takes an acute and aggressive course affecting relatively young individuals. Treatment of child ALL/LBL has much advanced. In contrast, advances for adults have been modest.

JCOG7801 and JCOG8101 revealed that T-LBL and ATL had a poor prognosis compared with other NHLs. Then, a Phase II study of a short-term, combination chemotherapy without maintenance therapy (JCOG8702) for LBL/ALL revealed that a fraction of adult patients with the disease were curable with a short-term, six-drug chemotherapy regimen (38). The next Phase II study (JCOG9004), G-CSF-supported, intensive post-remission chemotherapy and subsequent allo/auto-SCT, revealed that survival and PFS were improved from JCOG8702 in adult ALL and LBL (39). The next chemotherapeutic regimen with the intensified induction and post-remission chemotherapy with auto/allo-HSCT in JCOG9402 was feasible; however, this study failed to show improvements in long-term follow-up results when compared with the historical control JCOG9004 (40).

To further improve the therapeutic outcomes of adults with LBL/ALL, novel strategies are warranted such as risk-adapted treatment for bcr-abl-positive poor prognostic ALL with abl inhibitors. Partly because of the relatively low incidence of LBL/ALL, JCOG-LSG never activated clinical studies after JCO9402.

Hodgkin's Lymphoma

HL is the most chemo/radio-sensitive malignancy among malignant lymphomas, and clinical trials for the disease have steadily produced standard therapies. However, trials are less frequently conducted in Japan and other Asian countries because of a low incidence. Sequential Phase II studies for advanced HL (JCOG8905 and 9305) of C-MOPP (cyclophosphamide, vincristine, procarbazine and prednisone)/ABVd (doxorubicin, bleomycin, vinblastine and dacarbazine) and ABVd, respectively, both with a dose reduction of dacarbazine (250 mg/m^2) because of severe emesis in previous studies in Japanese, confirmed a similar efficacy to those from the USA and Europe (41–43). Safety and efficacy profiles of dacarbazine included in C-MOPP/ABVd and ABVd led to the approval of dacarbazine for clinical use covered through the National Health Insurance by MHLW in Japan without industrial trials.

The next Phase II study of ABV deleting dacarbazine with increased dose of doxorubicin followed by IF-RT (JCOG9705) revealed at the interim analysis that the 2-year PFS was significantly inferior to JCOG9305 (ABVd), suggesting that dacarbazine is a key agent for the treatment of HL (44).

A recent meta-analysis of the two JCOG studies in HL revealed two independent factors for OS, male and an elevated serum LDH, after a multivariate analysis (JCOG0108A) (45). Partly because of the low incidence of HL in Japanese, JCOG-LSG never conducted clinical studies after JCO9705. Recent studies from westerners revealed the efficacy of further risk-adaptive treatment for HL, lower dose of chemo/radio-therapy for those at low risk and more

intensive chemotherapy for those at high risk (46). New agents for HL include anti-CD30 monoclonal antibodies. Furthermore, therapy adjustment after an interim analysis of the response by F-fluorodeoxyglucose positron emission tomography–computed tomography (PET–CT) is now suggested. JCOG-LSG is now planning a new trial for HL including PET/CT scans.

Multiple Myeloma

MM is a progressive and incurable malignancy of plasma cells affecting mainly aged individuals. Alkylators and steroids have been the key drugs for remission induction, but MST was around 3 years without a plateau in the survival curve (47). A Phase II study of COP (cyclophosphamide, prednisolone)–MP (melphalan, prednisolone) for untreated overt MM patients (JCOG8906) revealed a similar efficacy to those from the USA and Europe (48). A subsequent randomized Phase III study comparing modified (m)COP-MP with/without ranimustine for untreated overt MM (JCOG9301) revealed that addition of ranimustine to mCOP/MP has no benefit for survival, despite improving the response rate and PFS, similar to findings of other studies evaluating the addition of new agents to alkylators and steroids in MM (49).

Both Phase III and II studies on untreated overt MM patients who were ineligible for HDC/auto-HSCT and eligible, respectively (JCOG0112 and JCOG0005-DI), were terminated early because of poor patient accrual and the results of a planned interim analysis, respectively (50). The planned interim analysis of JCOG0005-DI, when 16 of the 50 planned patients were enrolled, revealed that the primary endpoint, response rate, was less than the lower threshold associated with violation in two patients who underwent allo-HSCT instead of scheduled auto-SCT because of availability of HLA-matched sibling donors. Since 2000, several promising new agents have been incorporated in standard therapy for the disease (51). Following the results, LSG is now conducting a randomized Phase II study of bortezomib, a proteasome inhibitor, plus dexamethasone versus thalidomide, an immune modulator, plus dexamethasone for relapsed or refractory MM (JCOG0904).

Indolent B-cell NHL

Advanced FL and other low-grade B-cell lymphomas are clinically indolent but non-curable diseases in most patients. The prognosis for lymphomas has been improved by adding rituximab to chemotherapy (21). However, the optimal combination schedule of chemotherapy and rituximab has not been elucidated. We attempted to determine whether patients with indolent B-cell NHL would have long-term benefits from G-CSF-supported, dose-dense immune-chemotherapy which potentiates the antibody-dependent cell-mediated cytotoxicity of rituximab by comparing R-CHOP-21 versus R-CHOP-14 (JCOG0203) (52). However, the dose-dense strategy failed to improve PFS at the median follow-up time of 5.2 years. We are now planning to follow-up the patients enrolled in this study to further evaluate the long-term prognosis of this indolent disease and potential late complications including secondary malignancies.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a progressive, non-curable and relatively rare B-cell lymphoma derived from mantle zone B-cell with BCL1 translocation. In contrast to DLBCL and FL, addition of rituximab to CHOP did not improve the survival of MCL and HDC/ASCT has been reported as promising (53). Therefore, LSG is now conducting a single-arm Phase II study of R-high-CHOP followed by CHASER and HDC, LEED and auto-HSCT for previously untreated advanced-stage MCL (JCOG0406).

Localized Nasal NK/T-cell Lymphoma

Localized nasal NK/T-cell lymphoma is a refractory lymphoma relatively frequent in East Asia. Both the international project on PTCL and JCOG meta-analysis on T-NHL (JCOG0902A) revealed that the diagnosis of NK/T-cell lymphoma was poor (54,55). A Phase I/II study (JCOG0211-DI) of concurrent radiotherapy (50 Gy) and three courses of dexamethasone, etoposide, ifosfamide and carboplatin (DeVIC) consisting of multidrug resistance-non-related agents revealed that 2/3 dose of DeVIC and radiation was a safe and effective treatment when compared with a historical control of radiotherapy alone (56). A correlative study is ongoing to elucidate risk factors for relapse because PFS was not sufficient.

FUTURE ISSUES FOR JCOG-LSG

JCOG-LSG has conducted clinical trials for aggressive NHL since 1970, which has been divided into DLBCL, MCL, LBL/ALL, ATL and NK/T-NHL later, HL, MM and indolent-B-NHL, as shown in Fig. 1, to evaluate combined modality, dose intensification and incorporation of new agents in multidisciplinary treatment for lymphoid malignancies. LSG, now consisting of 47 institutions, is a relatively large group in JCOG, using much of the resources of the JCOG Data Center and Committees. JCOG-LSG initiated several studies independent from the JCOG-Data Center and supported by its own data center. However, numbers of patient enrollment in LSG have decreased in the last several years mainly due to the small number of ongoing trials. It takes longer to activate LSG protocols when compared with those by other cancer groups in JCOG mainly because of many disease entities, diverse prognosis and complex response criteria in each major disease entities, such as DLBCL, ATL and MM. Lymphoid malignancies are relatively rare; however, the spectrum is diverse consisting of 81

disease entities from indolent to aggressive in the WHO classification of 2008 (1). One way to conduct future LSG trials is to focus more on each disease entity as in the case of ATL and ENK/TML. The other is grouping the entities by treating modalities as in the case of several CD20-expressing low-grade B-cell lymphomas with rituximab-containing chemotherapy. It is desirable that clinical trials in LSG be based on disease entity, and if possible with risk grouping as in the case of trials for DLBCL and ATL. However, most of the diseases are rare and some of them take similar clinical courses including prognosis and response to therapies. On this issue, peripheral T-cell lymphomas other than ATL and T/NK ML, and low-grade B-cell lymphomas are the major two categories of disease-entity grouping.

Not only the complexity in lymphoma classification mentioned above, but also that in response criteria for lymphoma, ATL and MM which are, respectively, distinct from RECIST (response evaluation criteria in solid tumors) for other solid cancers has made the trials in LSG difficult. Recent revised criteria for lymphoma, which are applied in the JCOG0601 study, incorporating the PET/CT scan for decision of CR, might reduce the difficulty (57).

As described, JCOG-LSG has conducted clinical trials for establishing standard therapies. To keep and further upgrade the originality of JCOG-LSG trials in relation to similar cooperative study groups in the USA and Europe, several points are important including major target diseases, risk grouping for stratification and major phase of the trials. Since its establishment, JCOG-LSG has consecutively focused on diseases relatively common in Japan such as DLBCL, MM, ATL and NK/T-NHL. Recent advances in molecular-targeting therapy introduced many promising new agents for the diseases and other lymphoid malignancies. This promotes research on lymphoid malignancies for the early development of a new-standard combination therapy with the new agents in Japan. However, for the evaluation of new agent-combining treatment in Japan, JCOG-LSG should go side by side with those through industry-supported new agent trials to contribute to further improvement in the treatment of lymphoid malignancies with less lag from foreign developments. For instance, the highly advanced medical technology assessment system, which was enacted recently, would be one way of reducing the lag in Japan. Multigroup trials, including global ones and bridging studies, are another way.

Correlative studies in clinical trials have changed the next step of stratified treatments. For instance, ATL and T-LBL patients were excluded from subsequent JCOG trials for aggressive NHL since their clinical diagnosis was found to be poor in early trials (11–13). Future correlative studies in JCOG-LSG, retrospective and prospective and pathological and molecular analysis, should change the stratification of the clinical trials in future for risk-adaptive treatment. For that purpose, a banking system, which is now being established in JCOG for blood and tissue samples, is warranted. Fortunately, in the case of lymphoid malignancies, relatively easy access to samples of the neoplasm can promote correlative studies.

Lastly, as a member of cancer groups in JCOG, LSG will continue efforts to produce valuable and reliable evidence for the improvement of therapy for patients with lymphoid malignancies as rapidly as possible.

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Conflict of interest statement

None declared.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. *WHO Classification of Tumour of Haemaopoietic and Lymphoid Tissues*. 4th edn. Lyon: IARC Press 2008;281–4.
2. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. *Blood* 1977;50:481–92.
3. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci USA* 1980;77:7415–9.
4. Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc Natl Acad Sci USA* 1981;78:6476–80.
5. Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. *Proc Natl Acad Sci USA* 1982;79:2031–5.
6. Fisher RI. Advanced insights into the biology of malignant lymphomas. *J Clin Oncol* 2011;29:1799–800.
7. Richardson P. Multiple myeloma and amyloidosis: an evolving treatment paradigm toward the goal of tailored therapy. *J Clin Oncol* 2011;29:1801–2.
8. Shimoyama M, Fukuda H, Saijo N, Yamaguchi N. Japan Clinical Oncology Group (JCOG). *Jpn J Clin Oncol* 1998;28:158–62.
9. Tobinai K, Hotta T. Clinical trials for malignant lymphoma in Japan. *Jpn J Clin Oncol* 2004;34:369–78.
10. Fukuda H. Development of cancer cooperative groups in Japan. *Jpn J Clin Oncol* 2010;40:881–90.
11. Shimoyama M, Ichimaru M, Yunoki K, Oota K, Ogawa M. Final results of cooperative study of VEPA [vincristine, cyclophosphamide (endoxan), prednisolone and adriamycin] therapy in advanced adult non-Hodgkin's lymphoma: relation between T- or B-cell phenotype and response. *Jpn J Clin Oncol* 1982;12:227–37.

12. Shimoyama M, Ota K, Kikuchi M, Yunoki K, Konda S, Takatsuki K, et al. Chemotherapeutic results and prognostic factors of patients with advanced non-Hodgkin's lymphoma treated with VEPA or VEPA-M. *J Clin Oncol* 1988;6:128–41.
13. Tobinai K, Shimoyama M, Minato K, Shirakawa S, Kobayashi T, Hotta T, et al. Japan Clinical Oncology Group phase II trial of second-generation 'LSG4 protocol' in aggressive T- and B-lymphoma: a new predictive model for T-and B-lymphoma. *Proc Am Soc Clin Oncol* 1994;13:378a (Abstract).
14. Kinoshita T, Hotta T, Tobinai K, Kobayashi T, Ishizuka N, Tomonaga M, et al. A randomized controlled trial investigating the survival benefit of dose-intensified multidrug combination chemotherapy (LSG9) for intermediate- or high-grade non-Hodgkin's lymphoma: Japan Clinical Oncology Group Study 9002. *Int J Hematol* 2004;80:341–50.
15. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993;328:1002–6.
16. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993;329:987–94.
17. Ogura M, Kagami Y, Itoh K, Tobinai K, Fukuda H, Mukai K, et al. Standard CHOP therapy for low (L) or low-intermediate (L-I) risk patients (pts) with aggressive non-Hodgkin's lymphoma (NHL): A multicenter phase II study by Japan Clinical Oncology Group (JCOG 9508). *Proc Am Soc Hem* 2004;22:6703 (Abstract).
18. Itoh K, Ohtsu T, Fukuda H, Sasaki Y, Ogura M, Morishima Y, et al. Randomized phase II study of biweekly CHOP and dose-escalated CHOP with prophylactic use of lenograstim (glycosylated G-CSF) in aggressive non-Hodgkin's lymphoma: Japan Clinical Oncology Group Study 9505. *Ann Oncol* 2002;13:1347–55.
19. Hotta T, Shimakura Y, Ishizuka N, Fukuda H, Itoh K, Morishima Y, et al., The Lymphoma Study Group of the JCOG. Randomized phase III study of standard CHOP (S-CHOP) versus biweekly CHOP (Bi-CHOP) in aggressive non-Hodgkin's lymphoma (NHL): Japan Clinical Oncology Group study, JCOG 9809. *Proc Am Soc Clin Oncol* 2003;21:2271a (Abstract).
20. Ohmachi K, Tobinai K, Kobayashi Y, Itoh K, Nakata M, Shibata T, et al. Phase III trial of CHOP-21 versus CHOP-14 for aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG 9809. *Ann Oncol* 2011;22:1382–91.
21. Czuczman MS, Gregory SA. The future of CD20 monoclonal antibody therapy in B-cell malignancies. *Leuk Lymphoma* 2010;51:983–94.
22. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235–42.
23. Tobinai K, Igarashi T, Itoh K, Kobayashi Y, Taniwaki M, Ogura M, et al. Japanese multicenter phase II and pharmacokinetic study of rituximab in relapsed or refractory patients with aggressive B-cell lymphoma. *Ann Oncol* 2004;15:821–30.
24. Shipp MA, Abeloff MD, Antman KH, Carroll G, Hagenbeek A, Loeffler M, et al. International Consensus Conference on High-Dose Therapy with Hematopoietic Stem Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas: report of the jury. *J Clin Oncol* 1999;17:423–9.
25. Stiff PJ, Unger JM, Cook J, Constine LS, Couban S, Shea TC, et al. Randomized phase III U.S./Canadian intergroup trial (SWOG S9704) comparing CHOP ± R for eight cycles to CHOP ± R for six cycles followed by autotransplant for patients with high-intermediate (H-Int) or high IPI grade diffuse aggressive non-Hodgkin's lymphoma (NHL). *Proc Am Soc Clin Oncol* 2011;29:504a (Abstract).
26. Shimoyama M, Ota K, Kikuchi M, Yunoki K, Konda S, Takatsuki K, et al. Major prognostic factors of adult patients with advanced T-cell lymphoma/leukemia. *J Clin Oncol* 1988;6:1088–97.
27. Major prognostic factors of patients with adult T-cell leukemia-lymphoma: a cooperative study. Lymphoma Study Group (1984–1987). *Leuk Res* 1991;15:81–90.
28. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia–lymphoma: a report from the Lymphoma Study Group (1984–87). *Br J Haematol* 1991;79:428–37.
29. Tsukasaki K, Hermine O, Bazarbachi A, Ratner L, Ramos JC, Harrington W, Jr, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia–lymphoma: a proposal from an international consensus meeting. *J Clin Oncol* 2009;27:453–9.
30. Tobinai K, Shimoyama M, Inoue S, Takayasu S, Mikuni C, Kozuru M, et al. Phase I study of YK-176 (2-deoxycoformycin) in patients with adult T-cell leukemia–lymphoma. *Jpn J Clin Oncol* 1992;22:164–71.
31. Tsukasaki K, Tobinai K, Shimoyama M, Kozuru M, Uike N, Yamada Y, et al. Deoxycoformycin-containing combination chemotherapy for adult T-cell leukemia–lymphoma: Japan Clinical Oncology Group study (JCOG9109). *Int J Hematol* 2003;77:164–70.
32. Yamada Y, Tomonaga M, Fukuda H, Hanada S, Utsunomiya A, Tara M, et al. A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukemia-lymphoma (ATL): Japan Clinical Oncology Group (JCOG) Study 9303. *Br J Haematol* 2001;113:375–82.
33. Tsukasaki K, Utsunomiya A, Fukuda H, Shibata T, Fukushima T, Takatsuka Y, et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia–lymphoma: Japan Clinical Oncology Group Study JCOG9801. *J Clin Oncol* 2007;25:5458–64.
34. Gill PS, Harrington W, Kaplan MH, Ribeiro RC, Bennett JM, Liebman HA, et al. Treatment of adult T-cell leukemia–lymphoma with a combination of interferon alfa and zidovudine. *N Engl J Med* 1995;332:1744–8.
35. Hermine O, Blouscary D, Gessain A, Turlure P, Leblond V, Franck N, et al. Treatment of adult T-cell leukemia–lymphoma with zidovudine and interferon alfa. *N Engl J Med* 1995;332:1749–51.
36. Tobinai K, Kobayashi Y, Shimoyama M. Interferon alfa and zidovudine in adult T-cell leukemia–lymphoma. *N Engl J Med* 1995;333:1285–6 (Correspondence).
37. Bazarbachi A, Plumelle Y, Carlos Ramos J, Tortevoye P, Otrock Z, Taylor G, et al. Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. *J Clin Oncol* 2010;28:4177–83.
38. Kobayashi T, Tobinai K, Shimoyama M, Mikuni C, Konda S, Kozuru M, et al. Long-term follow-up results of adult patients with acute lymphocytic leukemia or lymphoblastic lymphoma treated with short-term, alternating non-cross-resistant chemotherapy: Japan Clinical Oncology Group Study 8702. Lymphoma Study Group. *Jpn J Clin Oncol* 1999;29:340–8.
39. Tobinai K, Takeyama K, Arima F, Aikawa K, Kobayashi T, Hanada S, et al. Phase II study of chemotherapy and stem cell transplantation for adult acute lymphoblastic leukemia or lymphoblastic lymphoma: Japan Clinical Oncology Group study 9004. *Cancer Science* 2007;98:1350–7.
40. Azuma T, Kensei Tobinai K, Takeyama K, Shibata T, Fukuda H, Kawano F, et al. Phase II study of chemotherapy (Cx) and stem cell transplantation (SCT) for adult acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL): long-term follow-up results of Japan Clinical Oncology Group (JCOG) Study 9402. *Proc Am Soc Hem* 2009;114:3087 (Abstract).
41. Takenaka T, Mikuni C, Miura A, Sasaki T, Suzuki H, Hotta T, et al. Alternating combination chemotherapy C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) and ABVd (adriamycin, bleomycin, vinblastine, dacarbazine) in clinical stage II–IV Hodgkin's disease: a multicenter phase II study (JCOG 8905). *Jpn J Clin Oncol* 2000;30:146–52.
42. Ogura M, Itoh K, Kinoshita T, Fukuda H, Takenaka T, Ohtsu T, et al. Phase II study of ABVd therapy for newly diagnosed clinical stage II–IV Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG 9305). *Int J Hematol* 2010;92:713–24.
43. Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992;327:1478–84.
44. Ogura M, Morishima Y, Itoh K, Ishizawa K, Kobayashi Y, Tobinai K, et al. Dacarbazine cannot be deleted from ABVD therapy for advanced Hodgkin lymphoma: Japan Clinical Oncology Group (JCOG) Study 9705. *Proc Am Soc Clin Oncol* 2003;22:573a (Abstract).
45. Itoh K, Kinoshita T, Watanabe T, Yoshimura K, Okamoto R, Chou T, et al. Prognostic analysis and a new risk model for Hodgkin lymphoma in Japan. *Int J Hematol* 2010;91:446–55.
46. Blum KA. Upcoming diagnostic and therapeutic developments in classical Hodgkin's lymphoma. *Hematology Am Soc Hematol Educ Program* 2010;2010:93–100.

47. Gregory WM, Richards MA, Malpas JS. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. *J Clin Oncol* 1992;10:334–42.
48. Takenaka T, Shirakawa S, Mikuni C, Sai T, Shimamoto Y, Araki K, et al. Alternating combination chemotherapy COP (cyclophosphamide, vincristine, prednisone) and MP (melphalan, prednisone) in multiple myeloma: a multicenter phase II study (JCOG8906). Lymphoma Study Group of the Japan Clinical Oncology Group. *Jpn J Clin Oncol* 1999;29:485–9.
49. Takenaka T, Itoh K, Suzuki T, Utsunomiya A, Matsuda S, Chou T, et al. Phase III study of ranimustine, cyclophosphamide, vincristine, melphalan, and prednisolone (MCNU-COP/MP) versus modified COP/MP in multiple myeloma: a Japan clinical oncology group study, JCOG 9301. *Int J Hematol* 2004;79:165–73.
50. Chou T, Tobinai K, Uike N, Asakawa T, Saito I, Fukuda H, et al. Melphalan–prednisolone and vincristine–doxorubicin–dexamethasone chemotherapy followed by prednisolone/interferon maintenance therapy for multiple myeloma: Japan Clinical Oncology Group Study, JCOG0112. *Jpn J Clin Oncol* 2011;41:586–9.
51. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med* 2011;364:1046–60.
52. Watanabe T, Tobinai K, Shibata T, Tsukasaki K, Morishima Y, Maseki N, et al. Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial. *J Clin Oncol* 2011;29:3990–8.
53. Williams ME, Connors JM, Dreyling MH, Gascoyne RD, Kahl BS, Leonard JP, et al. Mantle cell lymphoma: report of the 2010 Mantle Cell Lymphoma Consortium Workshop. *Leuk Lymphoma* 2011;52:24–33.
54. Vose J, Armitage J, Weisenburger D. International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol* 2008;26:4124–30.
55. Watanabe T, Kinoshita T, Itoh K, Yoshimura K, Ogura M, Kagami Y, et al. Pretreatment total serum protein is a significant prognostic factor for the outcome of patients with peripheral T/natural killer-cell lymphomas. *Leuk Lymphoma* 2010;51:813–21.
56. Yamaguchi M, Tobinai K, Oguchi M, Ishizuka N, Kobayashi Y, Isobe Y, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. *J Clin Oncol* 2009;27:5594–600.
57. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25:579–86.
58. Mizoroki F, Hirose Y, Sano M, Fukuda H, Tobinai K, Nakata M, et al. A phase II study of VEPA/EPPP chemotherapy for aggressive lymphoma in elderly patients: Japan Clinical Oncology Group Study JCOG9203. *Int J Hematol* 2006;83:55–62.
59. Yoshino T, Matsuno Y, Makamura S, Ohshima K, Mukai K, Kikuchi M, et al. Effectiveness of an educational program for improving the accuracy of histopathologic diagnosis of malignant lymphoma. *Proc Jpn Soc Lymphoreticular Tissue Res* 2003;43:88 (Abstract).

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Review Article

Clinical Trials and Treatment of ATL

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ATL is a distinct peripheral T-lymphocytic malignancy associated with human T-cell lymphotropic virus type I (HTLV-1). The diversity in clinical features and prognosis of patients with this disease has led to its subtype-classification into four categories, acute, lymphoma, chronic, and smoldering types, defined by organ involvement, and LDH and calcium values. In case of acute, lymphoma, or unfavorable chronic subtypes (aggressive ATL), intensive chemotherapy like the LSG15 regimen (VCAP-AMP-VECP) is usually recommended if outside of clinical trials, based on the results of a phase 3 trial. In case of favorable chronic or smoldering ATL (indolent ATL), watchful waiting until disease progression has been recommended, although the long-term prognosis was inferior to those of, for instance, chronic lymphoid leukemia. Retrospective analysis suggested that the combination of interferon alpha and zidovudine was apparently promising for the treatment of ATL, especially for types with leukemic manifestation. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is also promising for the treatment of aggressive ATL possibly reflecting graft versus ATL effect. 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.

1. Introduction

Adult T-cell leukemia-lymphoma (ATL) was first described in 1977 by Uchiyama et al. as a distinct clinico-pathological entity with a suspected viral etiology because of the clustering of the disease in the southwest region of Japan [1]. Subsequently, a novel RNA retrovirus, human T-cell leukemia/lymphotropic virus type I (HTLV-1), was isolated from a cell line established from leukemic cells of an ATL patient, and the finding of a clear association with ATL led to its inclusion among human carcinogenic pathogens [2–5]. In the mid-1980s and 1990s, several inflammatory diseases were reported to be associated with HTLV-1 [6–10]. At the same time, endemic areas for the virus and diseases have been found (reviewed in [11–13]). Diversity in ATL has been recognized and a classification of clinical subtypes of the disease was proposed [14]. This chapter will review the current recognition of ATL focusing on treatment of the disease.

2. Clinical Features and Laboratory Findings of ATL

ATL patients show a variety of clinical manifestations because of various complications of organ involvement by ATL cells, opportunistic infections and/or hypercalcemia [11–14]. These three often contribute to the extremely high mortality of the disease. Lymph node, liver, spleen, and skin lesions are frequently observed. Though less frequently, digestive tract, lungs, central nervous system, bone, and/or other organs may be involved. Large nodules, plaques, ulcers, and erythroderma are common skin lesions [15–17]. Immune suppression is common. Approximately 26% of 854 patients with ATL had active infections at diagnosis in a prior

nationwide study in Japan [14]. The incidence was highest in the chronic and smoldering types (36%) and lower in the acute (27%) and lymphoma types (11%). The infections were bacterial in 43%, fungal in 31%, protozoal in 18%, and viral in 8% of patients. The immunodeficiency at presentation in ATL patients can be exacerbated by cytotoxic chemotherapy. Individuals with indolent ATL might have no manifestation of the disease and are identified only by health checkups and laboratory examinations.

ATL cells are usually detected quite easily in the blood of affected individuals except for the smoldering type with mainly skin manifestations and lymphoma type [14]. These so-called "flower cells" have highly indented or lobulated nuclei with condensed chromatin, small or absent nucleoli, and a agranular and basophilic cytoplasm [18]. The histological analysis of aberrant cutaneous lesions or lymph nodes is essential for the diagnosis of the smoldering type with mainly skin manifestations and lymphoma type of ATL, respectively. Because ATL cells in the skin and lymph node can vary in size from small to large and in form from pleomorphic to anaplastic and Hodgkin-like cell with no specific histological pattern of involvement, differentiating between Sezary syndrome, other peripheral T-cell lymphomas and Hodgkin lymphoma versus ATL can at times be difficult without examinations for HTLV-1 serotype/genotype [13, 19].

Hypercalcemia is the most distinctive laboratory abnormality in ATL as compared to other lymphoid malignancies and is observed in 31% of patients (50% in acute type, 17% in lymphoma type, and 0% in the other two types) at onset [14]. Individuals with hypercalcemia do not usually have osteolytic bone lesions. Parathyroid hormone-related protein or receptor activator of nuclear factor kappa B ligand (RANKL) produced by ATL cells is considered the main factor causing hypercalcemia [20, 21].

Similar to serum LDH, β2-microglobulin, and serum thymidine kinase levels reflecting disease bulk/activity, the level of the soluble form of interleukin (IL)-2 receptor alpha-chain is elevated in the order of acute/lymphoma-type ATL, smoldering/chronic-type ATL, and HTLV-1 carriers as compared with normal individuals, perhaps with better accuracy than the other markers [22–24]. These serum markers are useful for detecting the acute transformation of indolent ATL as well as the early relapse of ATL after achieving responses by therapy.

Prototypical ATL cells have a mature alpha-beta T-cell phenotype, that is, they are terminal deoxynucleotidyl transferase- (TdT-)negative, cluster of differentiation (CD) 1a-negative, T-cell receptor alpha-beta positive, CD2-positive and CD5, CD45RO, and CD29-positive, and frequently do not express CD7 and CD26. A decline in the CD3 level with the appearance of CD25 indicates that the ATL cells are in an activated state. Most ATL cells are CD52-positive but some are negative, and this may correlate with the coexpression of CD30. About 90% of cases are CD4-positive and CD8-negative, and in rare cases either coexpress CD4 and CD8, are negative for both markers, or are only CD8-positive [25]. CC chemokine receptor 4 (CCR4) is expressed in more than 90% of cases and associated with a poor prognosis. Recent studies have suggested that the cells of some ATL may be the equivalent of regulatory T-cells because of the high frequency of expression of CD25/CCR4 and about half of FoxP3 [26–28].

3. Diagnosis of ATL

The diagnosis of typical ATL is not difficult and is based on clinical features, ATL cell morphology, mature helper-T-cell phenotype, and anti-HTLV-1 antibody in most cases [13]. Those rare cases, which might be difficult to diagnose, can be shown to have the monoclonal integration of HTLV-1 proviral DNA in the malignant cells as determined by Southern blotting. However, the monoclonal integration of HTLV-1 is also detected in some HAM/TSP patients and HTLV-1 carriers [29, 30]. After the diagnosis of ATL, subtype classification of the disease is necessary for the selection of appropriate treatment [14, 31].

4. Definition, Prognostic Factors, and Subtype Classification of ATL

ATL is a distinct peripheral T-lymphocytic malignancy associated with a retrovirus designated human T-cell leukemia virus type I or human T-cell lymphotropic virus type I (HTLV-1) [1, 11–14, 31].

Major prognostic indicators for ATL, which have been elucidated in 854 patients with ATL in Japan, the Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) by multivariate analysis, were advanced performance status (PS), high lactic dehydrogenase (LDH) level, age of 40 years or more, more than 3 involved lesions, and hypercalcemia [32]. Also a classification of clinical subtypes into acute, lymphoma, chronic, and smoldering types was proposed based on prognostic factors and clinical features of the disease [14]. The leukemic subtypes include all of the chronic type and most of the acute and smoldering types. The acute type has a rapid course with leukemic manifestation ($\geq$ 2% ATL cells) mostly, with or without lymphocytosis ($> 4 \times 109$/L) including ATL cells and most of the characteristic features of ATL-generalized lymphadenopathy, hepatosplenomegaly, skin involvement, other organ involvement, a high LDH value, and hypercalcemia. The symptoms and signs include abdominal pain, diarrhea, ascites, jaundice, unconsciousness, dyspnea, pleural effusion, cough, sputum, and chest X-ray abnormalities because of organ involvement, hypercalcemia, and/or opportunistic infections. The smoldering type shows an indolent course and 5% or more of leukemic cells in the peripheral blood without lymphocytosis but may include skin/lung involvement. The calcium level is less than the upper limit, and LDH level is less than 1.5 times the upper limit in smoldering ATL. The chronic type, with absolute lymphocytosis (4×109/L) less frequently showing flower cell morphology than the acute type, is frequently and occasionally associated with skin involvement and lymphadenopathy, respectively, and also usually shows a relatively indolent course. The calcium level is less than the upper limit, and the LDH level is less than double the upper limit of the chronic type. The lymphoma type presents with

the manifestations of a nodal-lymphoma without leukemic cells, frequently with high LDH/Ca levels, a rapid course, and symptoms and signs similar to the acute type. In case of ATL, clinical subtype is more important than Ann Arbor stage for predicting prognosis and deciding treatment because of frequent leukemic manifestation defined as stage IV.

Additional factors associated with a poor prognosis include thrombocytopenia, eosinophilia, bone marrow involvement, a high interleukin (IL)-5 serum-level, C-C chemokine receptor 4 (CCR4) expression, lung resistance-related protein (LRP), p53 mutation, and p16 deletion by multivariate analysis [26, 27, 33–37]. Specific for the chronic type of ATL, high LDH, high blood urea nitrogen (BUN), and low albumin levels were identified as factors for a poor prognosis by multivariate analysis [11]. Primary cutaneous tumoral type although generally included among smoldering ATL had a poor prognosis in univariate analysis [15].

5. Clinical Course, Treatment, and Response Criteria of ATL

Treatment decisions should be based on the ATL subtype-classification and the prognostic factors at onset including those related with ATL and comorbidity [31]. As mentioned above, subtype-classification of this disease has been proposed based on the prognosis and clinical manifestations. Without treatment, most patients with acute-/lymphoma/type ATL die of the disease or infections within weeks or months. More than half of patients with smoldering ATL survive for more than 5 years without chemotherapy and transformation to aggressive ATL. Chronic ATL has the most diverse prognosis among the subtypes and could be divided into favorable and unfavorable by clinical parameters (serum albumin, BUN, and LDH levels) after a multivariate analysis [31].

Current treatment options for ATL include watchful waiting until the disease progresses, interferon alpha (IFN) and zidovudine (AZT) therapy, multiagent chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT), and a new agent [15].

5.1. Watchful Waiting. At present, no standard treatment for ATL exists. Therefore, patients with the smoldering or favorable chronic type, who may survive one or more years without chemotherapy, excluding topical therapy for cutaneous lesions, should be observed and therapy should be delayed until progression of the disease [31]. However, it was recently found that the long-term prognosis of such patients was poorer than expected. In a long-term followup study for 78 patients with indolent ATL (favorable chronic- or smoldering-type) with a policy of watchful waiting until disease progression at a single institution, the median survival time was 5.3 years with no plateau in the survival curve. Twelve patients remained alive for > 10 years, 32 progressed to acute ATL, and 51 died [38]. Recently, the striking benefit of early intervention to indolent ATL by IFN and an antiretroviral agent was reported by a meta-analysis [39]. This modality should be extensively evaluated by larger clinical trials to establish appropriate management practices for indolent ATL.

5.2. Chemotherapy. Since 1978, chemotherapy trials have been consecutively conducted for patients newly diagnosed with ATL by JCOG's Lymphoma Study Group (LSG) (Table 1) [40–45]. Between 1981 and 1983, JCOG conducted a phase III trial (JCOG8101) to evaluate LSG1-VEPA (vincristine, cyclophosphamide, prednisone, and doxorubicin) versus LSG2-VEPA-M (VEPA plus methotrexate (MTX)) for advanced non-Hodgkin lymphoma (NHL), including ATL [40, 41]. The complete response (CR) rate of LSG2-VEPA-M for ATL (37%) was higher than that of LSG1-VEPA (17%; $P = .09$). However, the CR rate was significantly lower for ATL than for B-cell NHL and peripheral T-cell lymphoma (PTCL) other than ATL ($P < .001$). The median survival time of the 54 patients with ATL was 6 months, and the estimated 4-year survival rate was 8%.

In 1987, JCOG initiated a multicenter phase II study (JCOG8701) of a multiagent combination chemotherapy (LSG4) for advanced aggressive NHL (including ATL). LSG4 consisted of three regimens: (1) VEPA-B (VEPA plus bleomycin), (2) M-FEPA (methotrexate, vindesine, cyclophosphamide, prednisone, and doxorubicin), and (3) VEPP-B, (vincristine, etoposide, procarbazine, prednisone, and bleomycin) [42]. The CR rate for ATL patients was improved from 28% (JCOG8101) to 43% (JCOG8701); however, the CR rate was significantly lower in ATL than in B-cell NHL and PTCL ($P < .01$). Patients with ATL still showed a poor prognosis, with a median survival time of 8 months and a 4-year survival rate of 12%.

The disappointing results with conventional chemotherapies have led to a search for new active agents. Multicenter phase I and II studies of pentostatin (2′-deoxycoformycin, an inhibitor of adenosine deaminase) were conducted against ATL in Japan [43]. The phase II study revealed a response rate of 32% (10 of 31) in cases of relapsed or refractory ATL (2CRs and 8PRs).

These encouraging results prompted the investigators to conduct a phase II trial (JCOG9109) with a pentostatin-containing combination (LSG11) as the initial chemotherapy [44]. Patients with aggressive ATL—that is, of the acute, lymphoma, or unfavorable chronic type—were eligible for this study. Unfavorable chronic-type ATL, defined as having at least 1 of 3 unfavorable prognostic factors (low serum albumin level, high LDH level, or high BUN), has an unfavorable prognosis similar to that for acute- and lymphoma-type ATL. A total of 62 untreated patients with aggressive ATL (34 acute, 21 lymphoma, and 7 unfavorable chronic type) were enrolled. A regimen of 1 mg/m^2 vincristine on days 1 and 8, 40 mg/m^2 doxorubicin on day 1, 100 mg/m^2 etoposide on days 1 through 3, 40 mg/m^2 prednisolone (PSL) on days 1 and 2, and 5 mg/m^2 pentostatin on days 8, 15, and 22 was administered every 28 days for 10 cycles. Among the 61 patients evaluable for toxicity, four patients (7%) died of infections, two from septicemia, and two from cytomegalovirus pneumonia. Among the 60 eligible patients, there were 17CRs (28%) and 14 partial responses (PRs) (overall

Table 1: Results of sequential chemotherapeutic-trials of untreated patients with ATL (JCOG-LSG).

	J7801	J8101	J8701	J9109	J9303	JCOG9801	
	LSG1	LSG1/LSG2	LSG4	LSG11	LSG15	mLSG15/mLSG19	
Pts. No.	18	54	43	62	96	57	61
CR (%)	16.7	27.8	41.9	28.3	35.5	40.4	24.6
CR + PR (%)				51.6	80.6	72.0	65.6
MST (months)		7.5	8.0	7.4	13.0	12.7	10.9
2 yr. survival (%)				17.0	31.3		
3 yr. survival (%)				10.0	21.9	23.6	12.7
4 yr. survival (%)		8.0	11.6				

CR: complete remission, PR: partial remission, MST: median survival time.

response rate [ORR] = 52%). The median survival time was 7.4 months, and the estimated 2-year survival rate was 17%. The prognosis in patients with ATL remained poor, even though they were treated with a pentostatin-containing combination chemotherapy.

In 1994, JCOG initiated a phase II trial (JCOG9303) of an eight-drug regimen (LSG15) consisting of vincristine, cyclophosphamide, doxorubicin, prednisone, ranimustine, vindesine, etoposide, and carboplatin for untreated ATL [45]. Dose intensification was attempted with the prophylactic use of granulocyte colony-stimulating factor (G-CSF). In addition, non-cross-resistant agents, such as ranimustine and carboplatin, and intrathecal prophylaxis with MTX and PSL were incorporated. Ninety-six previously untreated patients with aggressive ATL were enrolled: 58 acute, 28 lymphoma, and 10 unfavorable chronic types. Approximately 81% of the 93 eligible patients responded (75/93), with 33 patients obtaining a CR (35%). The overall survival rate of the 93 patients at 2 years was estimated to be 31%, with a median survival time of 13 months. Grade 4 neutropenia and thrombocytopenia were observed in 65% and 53% of the patients, respectively, whereas grade 4 nonhematologic toxicity was observed in only one patient.

Dose intensification of CHOP with prophylactic use of G-CSF was expected to improve survival among patients with aggressive NHL, and our randomized phase II study (JCOG9505) comparing CHOP-14 (LSG19) and dose-escalated CHOP (LSG20) to treat aggressive NHL excluding ATL revealed biweekly CHOP to be more promising [46]. Therefore, we regarded biweekly CHOP as a standard treatment for NHL including aggressive ATL at the time of designing this phase III study.

To confirm whether the LSG15 regimen is a new standard for the treatment of aggressive ATL, JCOG conducted a phase III trial comparing modified (m)-LSG15 with biweekly CHOP (cyclophosphamide, hydroxy-doxorubicin, vincristine [Oncovin], and prednisone), both supported with G-CSF and intrathecal prophylaxis [47].

mLSG19, a modified version of LSG19, consisted of eight cycles of CHOP [CPA 750 mg/m^2, ADM 50 mg/m^2, VCR 1.4 mg/m^2 (maximum 2 mg) on day 1 and PSL 100 mg on days 1 to 5] every 2 weeks [46]. The modification was an intrathecal administration identical to that in mLSG15.

mLSG15 in JCOG9801 was a modified version of LSG15 in JCOG9303, consisting of three regimens: VCAP [VCR 1 mg/m^2 (maximum 2 mg), CPA 350 mg/m^2, ADM 40 mg/m^2, PSL 40 mg/m^2] on day 1, AMP [ADM 30 mg/m^2, MCNU 60 mg/m^2, PSL 40 mg/m^2] on day 8, and VECP [VDS 2.4 mg/m^2 on day 15, ETP 100 mg/m^2 on days 15 to 17, CBDCA 250 mg/m^2 on day15, PSL 40 mg/m^2 on days 15 to 17] on days 15–17, and the next course was to be started on day 29 (Figure 1). The modifications in mLSG15 as compared to LSG15 were as follows: (1) The total number of cycles was reduced from 7 to 6 because of progressive cytopenia, especially thrombocytopenia, after repeating the LSG15 therapy. (2) Cytarabine 40 mg was used with MTX 15 mg and PSL 10 mg for prophylactic intrathecal administration, at the recovery phases of courses 1, 3, and 5 because of the high frequency of central nervous system relapse in the JCOG9303 study. Untreated patients with aggressive ATL were assigned to receive either six courses of mLSG15 every 4 weeks or eight courses of biweekly CHOP. The primary endpoint was overall survival. A total of 118 patients were enrolled. The CR rate was higher in the mLSG15 arm than in the biweekly CHOP arm (40% versus 25%, resp.; P = .020). As shown in Table 1, the median survival time and OS rate at 3 years were 12.7 months and 24% in the mLSG15 arm and 10.9 months and 13% in the biweekly CHOP arm [two-sided P = .169, and the hazard ratio was 0.75; 95% confidence interval (CI), 0.50 to 1.13]. A Cox regression analysis with performance status (PS 0 versus 1 versus 2–4) as the stratum for baseline hazard functions was performed to evaluate the effect on overall survival of age, B-symptoms, subtypes of ATL, LDH, BUN, bulky mass, and treatment arms. According to this analysis, the hazard ratio and two-sided P value for the treatment arms were 0.62 (95% CI, 0.38 to 1.01) and .056, respectively. The difference between the crude analysis and this result was because of unbalanced prognostic factors, such as PS 0 versus 1, and the presence or absence of bulky lesions between the treatment arms. The progression-free

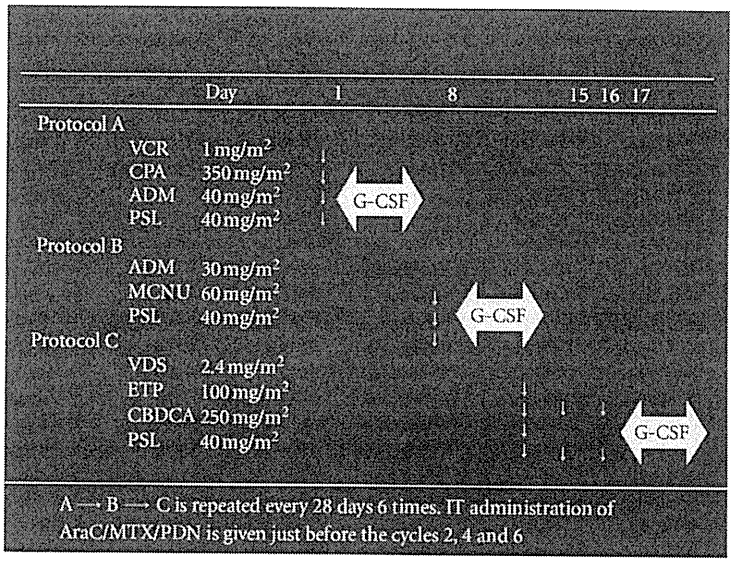

FIGURE 1: Regimen of VCAP-AMP-VECP in mLSG15. VCAP: vincristine (VCR), cyclophosphamide (CPA), doxorubicin (ADM), prednisone (PSL); AMP: ADM, ranimustine (MCNU), PSL; VECP: vindesine (VDS), etoposide (ETP), carboplatin (CBDCA), and PSL. *) MCNU and VDS are nitrosourea and vinca alkaloid, respectively, developed in Japan. A previous study on myeloma described that carmustine (BCNU), another nitrosourea, at 1 mg/kg is equivalent to MCNU at 0.8 to 1.0 mg/kg. VDS at 2.4 mg/m^2 can be substituted for VCR, another vinca alkaloid used in this regimen, at 1 mg/m^2 with possibly less myelosuppression and more peripheral neuropathy which can be managed by dose modification.

survival rate at 1 year was 28% in the mLSG15 arm compared with 16% in the biweekly CHOP arm (two-sided $P = .20$).

In mLSG15 versus mLSG19, rate of grade 4 neutropenia, grade 4 thrombocytopenia, and grade 3/4 infection were 98% versus 83%, 74% versus 17%, and 32% versus 15%, respectively. There were three toxic deaths in the former. Three treatment-related deaths (TRDs), two from sepsis and one from interstitial pneumonitis related to neutropenia, were reported in the mLSG15 arm. Two cases of myelodysplastic syndrome were reported, one each in both arms.

The longer survival at 3 years and higher CR rate with mLSG15 compared with mLSG19 suggest that mLSG15 is a more effective regimen at the expense of higher toxicity, providing the basis for future investigations in the treatment of ATL [47]. The superiority of VCAP-AMP-VECP in mLSG15 to biweekly CHOP in mLSG19 may be explained by the more prolonged, dose dense schedule of therapy in addition to 4 more drugs. In addition, agents such as carboplatin and ranimustine not affected by multidrug-resistance (MDR) related genes, which were frequently expressed in ATL cells at onset, were incorporated [48]. Intrathecal prophylaxis, which was incorporated in both arms of the phase III study, should be considered for patients with aggressive ATL even in the absence of clinical symptoms because a previous analysis revealed that more than half of relapses at new sites after chemotherapy occurred in the CNS [49]. However, the median survival time of 13 months in VCAP-AMP-VECP (LSG15/mLSG15) still compares unfavorably to other hematological malignancies, requiring further effort to improve the outcome.

5.3. Interferon-Alpha and Zidovudine. A small phase II trial in Japan of IFN alpha against relapsed/refractory ATL showed a response rate (all PR) of 33% (8/24), including 5 out of 9 (56%) chronic-type ATL [50]. In 1995, Gill and associates reported that 11 of 19 patients with acute- or lymphoma-type ATL showed major responses (5 CR and 6 PR) to a combination of interferon-alpha (IFN) and zidovudine (AZT) [51]. The efficacy of this combination was also observed by Hermine and associates; major objective responses were obtained in all five patients with ATL (four with acute type and one with smoldering type) [52]. Although these results are encouraging, the OS of previously untreated patients with ATL was relatively short (4.8 months) compared with the survival of those in the chemotherapy trials conducted by the JCOG-LSG (7 to 8 months) [53]. After that, numerous small phase II studies using AZT and IFN have shown responses in ATL patients [54–56]. High doses of both agents are recommended: 6–9 million units of IFN in combination with daily divided AZT doses of 800–1000 mg/day. Therapeutic effect of AZT and IFN is not through a direct cytotoxic effect of these drugs on the leukemic cells [57]. Enduring AZT treatment of ATL cell lines results in inhibition of telomerase which reprograms the cells to p53-dependent senescence [58].

Recently, the results of a "meta-analysis" on the use of IFN and AZT for ATL were reported [39]. A total of 100 patients received interferon-alpha and AZT as initial treatments. The ORR was 66%, with a 43% CR rate. In this worldwide retrospective analysis, the median survival time was 24 months and the 5-year survival rate was 50% for

first-line IFN and AZT, versus 7 months and 20% for 84 patients who received first-line chemotherapy. The median survival time of patients with acute-type ATL treated with first-line IFN/AZT and chemotherapy was 12 and 9 months, respectively. Patients with lymphoma-type ATL did not benefit from this combination. In addition, first-line IFN/AZT therapy in chronic- and smoldering-type ATL resulted in a 100% survival rate at a median followup of 5 years. However, because of the retrospective nature of this meta-analysis based on medical records at each hospital, the decision process to select the therapeutic modality for each patient and the possibility of interference with OS by second-line treatment remains unknown. While the results for IFN/AZT in indolent ATL appear to be promising compared to those with watchful-waiting policy until disease progression, recently reported from Japan [38], the possibility of selection bias cannot be ruled out. A prospective multicenter phase III study evaluating the efficacy of IFN/AZT as compared to watchful-waiting for indolent ATL is to be initiated in Japan.

Recently, a phase II study of the combination of arsenic trioxide, IFN, and AZT for chronic ATL revealed an impressive response rate and moderate toxicity [39]. Although the results appeared promising, the addition of arsenic trioxide to IFN/AZT, which might be sufficient for the treatment of chronic ATL as described above, caused more toxicity and should be evaluated with caution.

5.4. Allogeneic Hematopoietic Stem-Cell Transplantation (Allo-HSCT). Allo-HSCT is now recommended for the treatment of young patients with aggressive ATL [31, 59]. Despite higher treatment-related mortality including graft versus host disease in a retrospective multicenter analysis of myeloablative allo-HSCT, the estimated 3-year OS of 33% is promising, possibly reflecting a graft versus ATL effect [60]. To evaluate the efficacy of allo-HSCT more accurately, especially in view of a comparison with intensive chemotherapy, a prospective multicenter phase II study of LSG15 chemotherapy followed by allo-HSCT is ongoing (JCOG0907).

Feasibility studies of allo-HSCT with reduced intensity conditioning for relatively aged patients with ATL also revealed promising results, and subsequent multicenter trials are being conducted in Japan [61, 62]. The minimal residual disease after allo-HSCT detected as HTLV-1 proviral load was much less than that after chemotherapy or AZT/IFN therapy, suggesting the presence of a graft-versus-ATL effect as well as graft-versus-HTLV-1 activity [61].

It remains unclear which type of allo-HSCT (myeloablative or reduced intensity conditioning) is more suitable for the treatment of ATL. Furthermore, selection criteria with respect to responses to previous treatments, sources of stem cells, and HTLV-1 viral status of the donor remain to be determined. Recently, a patient in whom ATL derived from donor cells developed four months after transplantation of stem cells from a sibling with HTLV-I was reported [63].

However, several other retrospective studies as well as those mentioned above on allo-HSCT showed a promising long-term survival rate of 20 to 40% with an apparent plateau phase despite significant treatment-related mortality.

5.5. Supportive Care. The prevention of opportunistic infections is essential in the management of ATL patients, nearly half of whom develop severe infections during chemotherapy. Some patients with indolent ATL develop infections during watchful waiting.

Sulfamethoxazole/trimethoprim and antifungal agents have been recommended as prophylaxes for Pneumocystis jiroveci pneumonia and fungal infections, respectively, in the JCOG trials [43–45]. While cytomegalovirus infections are not infrequent among ATL patients, ganciclovir is not usually recommended as a prophylaxis [31]. In addition, in patients not receiving chemotherapy or allo-HSCT, antifungal prophylaxis may not be critical. An antistrongyloides agent, such as ivermectin or albendazole, should be considered to avoid systemic infections in patients with a history of exposure to the parasite in the tropics. Treatment with steroids and proton pump inhibitors may precipitate a fulminant strongyloides infestation and warrants testing before these agents are used in endemic areas [31]. Hypercalcemia associated with aggressive ATL can be corrected using chemotherapy in combination with hydration and bisphosphonate even when the performance status of the patient is poor.

5.6. Response Criteria. The complex nature of ATL, often with both leukemic and lymphomatous components, makes response assessment difficult. A modification of the JCOG response criteria was suggested by ATL consensus-meeting reflecting those for CLL and NHL which had been published later [31, 64, 65]. Recently, revised response criteria were proposed for lymphoma. New guidelines were presented incorporating positron emission tomography (PET), especially for the assessment of CR. It is well known and described in the criteria that several kinds of lymphoma including peripheral T-cell lymphomas were variably [18F] fluorodeoxyglucose (FDG) avid [66]. Meanwhile, PET or PET/CT is recommended for evaluations of response when the tumorous lesions are FDG-avid at diagnosis [31].

5.7. New Agents for ATL

5.7.1. Purine Analogs. Several purine analogs have been evaluated for ATL. Among them, pentostatin (deoxycoformycin) has been most extensively evaluated as a single agent and in combination as described above [43, 46].

Other purine analogs clinically studied for ATL are fludarabine and cladribine. Fludarabine is among standard treatments for B-chronic lymphocytic leukemia and other lymphoid malignancies. In a phase I study of fludarabine in Japan, 5 ATL patients and 10 B-CLL patients with refractory or relapsed-disease were enrolled [67]. Six grade 3 nonhematological toxicities were only observed in the ATL patients. PR was achieved only in one of the 5 ATL patients and the duration was short. Cladribine is among standard treatments for hairy cell leukemia and other lymphoid malignancies. A phase II study of cladribine for relapsed/refractory aggressive-ATL in 15 patients revealed only one PR [68].

Forodesine, a purine nucleotide phosphorylase (PNP) inhibitor, is among purine nucleotide analogs. PNP is an

enzyme in the purine salvage pathway that phosphorolysis 2′deoxyguanosine (dGuo). Purine nucleoside phosphorylase (PNP) deficiency in humans results in a severe combined immunodeficiency phenotype and the selective depletion of T cells associated with high plasma deoxyguanosine (dGuo) and high intracellular deoxyguanosine triphosphate levels in those cells with high deoxynucleoside kinase activity such as T cells, leading to cell death. Inhibitors of PNP, such as forodesine, mimic SCID in vitro and in vivo, suggesting a new targeting agent specific for T cell malignancies [69]. A dose escalating phase I study of forodesine is being conducted in Japan for T cell malignancies including ATL.

5.7.2. Histone Deacetylase Inhibitor. Gene expression governed by epigenetic changes is crucial to the pathogenesis of cancer. Histone deacetylases (HDACs) are enzymes involved in the remodeling of chromatin and play a key role in the epigenetic regulation of gene expression. Deacetylase inhibitors (DACis) induce the hyperacetylation of nonhistone proteins as well as nucleosomal histones resulting in the expression of repressed genes involved in growth arrest, terminal differentiation, and/or apoptosis among cancer cells. Several classes of HDACi have been found to have potent anticancer effects in preclinical studies. HDACIs such as vorinostat (suberoylanilide hydroxamic acid: SAHA), romidepsin (depsipeptide), and panobinostat (LBH589) have also shown promise in preclinical and/or clinical studies against T-cell malignancies including ATL [70, 71]. Vorinostat and romidepsin have been approved for cutaneous T-cell lymphoma (CTCL) by the Food and Drug Administration in the USA. LBH589 has a significant anti-ATL effect in vitro and in mice [71]. However, a phase II study for CTCL and indolent ATL in Japan was terminated because of severe infections associated with the shrinkage of skin tumors and formation of ulcers in patients with ATL. Further study is required to evaluate the efficacy of HDACIs for PTCL/CTCL including ATL.

5.7.3. Monoclonal Antibodies and Toxin Fusion Proteins. Monoclonal antibodies (MoAb) and toxin fusion proteins targeting several molecules expressed on the surface of ATL cells and other lymphoid malignant cells, such as CD25, CD2, CD52, and chemokine receptor 4 (CCR4), have shown promise in recent clinical trials.

Because most ATL cells express the alpha-chain of IL-2R (CD25), Waldmann et al. treated patients with ATL using monoclonal antibodies to CD25 [72]. Six (32%) of 19 patients treated with anti-Tac showed objective responses lasting from 9 weeks to longer than 3 years. One impediment to this approach is the quantity of soluble IL-2R shed by the tumor cells into the circulation. Another strategy for targeting IL-2R is conjugation with an immunotoxin (Pseudomonas exotoxin) or radioisotope (yttrium-90). Waldmann et al. developed a stable conjugate of anti-Tac with yttrium-90. Among the 16 patients with ATL who received 5- to 15-mCi doses, 9 (56%) showed objective responses. The response lasted longer than that obtained with unconjugated anti-Tac antibody [73, 74].

LMB-2, composed of the anti-CD25 murine MoAb fused to the truncated form of Pseudomonas toxin, was cytotoxic to CD25-expressing cells including ATL cells in vitro and in mice. Phase I/II trials of this agent showed some effect against hairy cell leukemia, CTCL, and ATL [6]. Six of 35 patients in the phase I study had significant levels of neutralizing antibodies after the first cycle. This drug deserves further clinical trials including in combination with cytotoxic agents.

Denileukin diftitox (DD; DAB(389)-interleukin-2 [IL-2]), an interleukin-2-diphtheria toxin fusion protein targeting IL-2 receptor-expressing malignant T lymphocytes, shows efficacy as a single agent against CTCL and peripheral T-cell lymphoma (PTCL) [75]. Also the combination of this agent with multiagent chemotherapy, CHOP, was promising for PTCL [76]. ATL cells frequently and highly express CD25 as described above, and several ATL cases successfully treated with this agent have been reported [77].

CD52 antigen is present on normal and pathologic B and T cells. In PTCL, however, CD52 expression varies among patients, with an overall expression rate lower than 50% in one study but not in another [78, 79]. ATL cells frequently express CD52 as compared to other PTCLs. The humanized anti-CD52 monoclonal antibody alemtuzumab is active against CLL and PTCL as a single agent. The combination of alemtuzumab with a standard-dose cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) regimen as a first-line treatment for 24 patients with PTCL showed promising results with CR in 17 (71%) patients; 1 had a partial remission, with an overall median duration of response of 11 months and was associated with mostly manageable infections but including CMV reactivation [80]. Major infections were Jacob-Creutzfeldt virus reactivation, pulmonary invasive aspergillosis, and staphylococcus sepsis.

ATL cells express CD52, the target of alemtuzumab, which was active in a preclinical model of ATL and toxic to p53-deficient cells, and several ATL cases successfully treated with this agent have been reported [81–83].

Siplizumab is a humanized MoAb targeting CD2 and showed efficacy in a murine ATL model. P1 dose-escalating study of this agent in 22 patients with several kinds of T/NK-cell malignancy revealed 6 responses (2 CR in LGL leukemia, 3 PR in ATL, and 1 PR in CTCL). However, 4 patients developed EBV-associated LPD [84]. The broad specificity of this agent may eliminate both CD4- and CD8-positive T cells as well as NK cells without effecting B cells and predispose individuals to the development of EBV lymphoproliferative syndrome.

CC chemokine receptor 4 (CCR4) is expressed on normal T helper type 27 and regulatory T (Treg) cells and on certain types of T-cell neoplasms [20, 21, 35]. KW-0761, a next generation humanized anti-CCR4 mAb, with a defucosylated Fc region, exerts strong antibody-dependent cellular cytotoxicity (ADCC) due to increased binding to the Fcγ receptor on effecter cells [85]. A phase I study of dose escalation with 4 weekly intravenous infusions of KW-0761 in 16 patients with relapsed CCR4-positive T cell malignancy (13 ATL and 3 PTCL) revealed that one patient, at the maximum dose (1.0 mg/kg), developed grade (G) 3 dose-limiting toxic effects, namely, skin rashes and febrile

Table 2: Strategy for the treatment of Adult T-Cell Leukemia-Lymphoma.

Smoldering- or favorable chronic-type ATL
(i) Consider inclusion in prospective clinical trials.
(ii) Symptomatic patients (skin lesions, opportunistic infections, etc.): Consider AZT/IFN or Watch and Wait.
(iii) Asymptomatic patients: Consider Watch and Wait.
Unfavorable chronic- or acute-type ATL
(i) If outside clinical trials, check prognostic factors (including clinical and molecular factors if possible):
(a) Good prognostic factors: consider chemotherapy (VCAP-AMP-VECP evaluated by a phase III trial against biweekly-CHOP) or AZT/IFN (evaluated by a meta-analysis on retrospective studies).
(b) Poor prognostic factors: consider chemotherapy followed by conventional or reduced intensity allo-HSCT (evaluated by retrospective and prospective Japanese analyses, resp.).
(c) Poor response to initial therapy: Consider conventional or reduced intensity allo-HSCT.
Lymphoma-type ATL
(i) If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP).
(ii) Check prognostic factors (including clinical and molecular factors if possible) and response to chemotherapy:
(a) Good prognostic factors and good response to initial therapy: Consider chemotherapy followed by observation.
(b) Poor prognostic factors or poor response to initial therapy: Consider chemotherapy followed by conventional or reduced intensity allo-HSCT.

neutropenia and G4 neutropenia [86]. Other treatment-related G3-4 toxic effects were lymphopenia ($n = 10$), neutropenia ($n = 3$), leukopenia ($n = 2$), herpes zoster ($n = 1$), and acute infusion reaction/cytokine release syndrome ($n = 1$). Neither the frequency nor severity of these effects increased with dose escalation or the plasma concentration of the agent. The maximum tolerated dose was not reached. No patients had detectable levels of anti-KW-0761 antibody. Five patients (31%; 95% CI, 11% to 59%) achieved objective responses: 2 complete (0.1; 1.0 mg/kg) and 3 partial (0.01; 2 at 1.0 mg/kg) responses. Three out of 13 patients with ATL (31%) achieved a response (2 CR and 1 PR). Responses in each lesion were diverse, that is, good in PB (6 CR and 1 PR/7 evaluable cases), intermediate in skin (3 CR and 1 PR/8 evaluable cases), and poor in LN (1 CR and 2 PR/11 evaluable cases). KW-0761 was well tolerated at all the doses tested, demonstrating potential efficacy against relapsed CCR4-positive ATL or PTCL. Recently, results of subsequent phase II studies at the 1.0 mg/kg in relapsed ATL, showing 50% of response rate with acceptable toxicity profiles, reported [87]. A phase II trial of single agent KW-0761 at the 1.0 mg/kg in relapsed PTCL/CTCL and a phase II trial of VCAP-AMP-VECP combined with KW-0761 for untreated aggressive ATL are ongoing.

5.7.4. Other Agents. A proteasome inhibitor, bortezomib (Velcade), and an immunomodulatory agent, lenalidomide (Revlimid), both have potent preclinical and clinical activity in T-cell malignancies including ATL, are now under clinical trials for relapsed ATL in Japan [88–90]. Other potential drugs for ATL include pralatrexate (Folotyn), a new agent with clinical activity in T-cell malignancies including ATL [91–93]. The agent is a novel antifolate with improved membrane transport and polyglutamylation in tumor cells and high affinity for the reduced folate carrier (RFC) highly expressed in malignant cells and has been approved by FDA recently for T-cell lymphoma including ATL.

5.8. Prevention. Two steps should be considered for the prevention of HTLV-1-associated ATL. The first is the prevention of HTLV-1 infections. This has been achieved in some endemic areas in Japan by screening for HTLV-1 among blood donors and asking mothers who are carriers to refrain from breast feeding. For several decades, before initiation of the interventions, the prevalence of HTLV-1 has declined drastically in endemic areas in Japan, probably because of birth cohort effects [94]. The elimination of HTLV-1 in endemic areas is now considered possible due to the natural decrease in the prevalence as well as the intervention of transmission through blood transfusion and breast feeding. The second step is the prevention of ATL among HTLV-1 carriers. This has not been achieved partly because only about 5% of HTLV-1 carriers develop the disease in their life time although several risk factors have been identified by a cohort study of HTLV-1 carriers (Joint Study of Predisposing Factors for ATL Development) [95]. Also, no agent has been found to be effective in preventing the development of ATL among HTLV-1 carriers.

6. Conclusions

Clinical trials have been paramount to the recent advances in ATL treatment, including assessments of chemotherapy, AZT/IFN, and allo-HSCT. Recently, a strategy for ATL treatment, stratified by subtype-classification, prognostic factors, and the response to initial treatment as well as response criteria, was proposed [31]. The recommended treatment algorithm for ATL is shown in Table 2. However, ATL still has a worse prognosis than the other T-cell malignancies [96].There is no plateau with an initial steep slope and subsequent gentle slope without a plateau in the survival curve for aggressive or indolent ATL treated by watchful waiting and with chemotherapy, respectively, although the prognosis is much better in the latter [38]. A prognostic model for

each subgroup should be elucidated to properly identify the candidate for allo-HSCT which can achieve a cure of ATL despite considerable treatment-related mortality. Although several small phase II trials and a recent metaanalysis suggested IFN/AZT therapy to be promising, no confirmative phase III study has been conducted [39]. Furthermore, as described in the other chapters in detail, more than ten promising new agents for PTCL/CTCL including ATL are now in clinical trials or preparation. Future clinical trials on ATL as described above should be incorporated to ensure that the consensus is continually updated to establish evidence-based practical guidelines.

References

[1] T. Uchiyama, J. Yodoi, and K. Sagawa, "Adult T-cell leukemia: clinical and hematologic features of 16 cases," *Blood*, vol. 50, no. 3, pp. 481–492, 1977.

[2] B. J. Poiesz, F. W. Ruscetti, and A. F. Gazdar, "Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 77, no. 12, pp. 7415–7419, 1980.

[3] Y. Hinuma, K. Nagata, and M. Hanaoka, "Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 78, no. 10 I, pp. 6476–6480, 1981.

[4] I. Miyoshi, I. Kubonishi, and S. Yoshimoto, "Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells," *Nature*, vol. 294, no. 5843, pp. 770–771, 1981.

[5] M. Yoshida, I. Miyoshi, and Y. Hinuma, "Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 79, no. 6 I, pp. 2031–2035, 1982.

[6] A. Gessain, F. Barin, and J. C. Vernant, "Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis," *The Lancet*, vol. 2, no. 8452, pp. 407–410, 1985.

[7] M. Osame, K. Usuku, and S. Izumo, "HTLV-I associated myelopathy, a new clinical entity," *The Lancet*, vol. 1, no. 8488, pp. 1031–1032, 1986.

[8] L. LaGrenade, B. Hanchard, V. Fletcher, B. Cranston, and W. Blattner, "Infective dermatitis of Jamaican children: a marker for HTLV-I infection," *The Lancet*, vol. 336, no. 8727, pp. 1345–1347, 1990.

[9] M. Mochizuki, T. Watanabe, K. Yamaguchi et al., "HTLV-I uveitis: a distinct clinical entity caused by HTLV-I," *Japanese Journal of Cancer Research*, vol. 83, no. 3, pp. 236–239, 1992.

[10] K. Terada, S. Katamine, K. Eguchi et al., "Prevalence of serum and salivary antibodies to HTLV-1 in Sjogren's syndrome," *The Lancet*, vol. 344, no. 8930, pp. 1116–1119, 1994.

[11] K. Takatsuki, *Adult T-cell Leukemia*, Oxford University Press, New York, NY, USA, 1994.

[12] "IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: human immunodeficiency viruses and human T-cell lymphotropic viruses," in *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, IARC Press, Geneva, Switzerland, 1996.

[13] K. Ohshima, E. S. Jaffe, and M. Kikuchi, "Adult T-cell leukemia/lymphoma," in *WHO Classification of Tumour of Haemaopoietic and Lymphoid Tissues*, S. H. Swerdlow, E. Campo, N. L. Harris et al., Eds., pp. 281–284, IARC Press, Lyon, France, 4th edition, 2008.

[14] M. Shimoyama, "Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the lymphoma study group (1984-87)," *British Journal of Haematology*, vol. 79, no. 3, pp. 428–437, 1991.

[15] A. L. Bittencourt, M. D. G. Vieira, C. R. Brites, L. Farre, and H. S. Barbosa, "Adult T-cell leukemia/lymphoma in Bahia, Brazil: analysis of prognostic factors in a group of 70 patients," *American Journal of Clinical Pathology*, vol. 128, no. 5, pp. 875–882, 2007.

[16] M. Amano, M. Kurokawa, K. Ogata, H. Itoh, H. Kataoka, and M. Setoyama, "New entity, definition and diagnostic criteria of cutaneous adult T-cell leukemia/lymphoma: human T-lymphotropic virus type 1 proviral DNA load can distinguish between cutaneous and smoldering types," *Journal of Dermatology*, vol. 35, no. 5, pp. 270–275, 2008.

[17] Y. Sawada, R. Hino, K. Hama et al., "Type of skin eruption is an independent prognostic indicator for adult T-cell leukemia/lymphoma," *Blood*, vol. 117, no. 15, pp. 3961–3967, 2011.

[18] J. M. Bennett, D. Catovsky, M. T. Daniel et al., "Proposals for the classification of chronic (mature) B and T lymphoid leukaemias," *Journal of Clinical Pathology*, vol. 42, no. 6, pp. 567–584, 1989.

[19] K. Lennert, M. Kikuchi, and E. Sato, "HTLV-positive and -negative T-cell lymphomas. Morphological and immunohistochemical differences between European and HTLV-positive Japanese T-cell lymphomas," *International Journal of Cancer*, vol. 35, no. 1, pp. 65–72, 1985.

[20] T. Watanabe, K. Yamaguchi, K. Takatsuki, M. Osame, and M. Yoshida, "Constitutive expression of parathyroid hormone-related protein gene in human T cell leukemia virus type 1 (HTLV-1) carriers and adult T cell leukemia patients that can be trans-activated by HTLV-1 tax gene," *Journal of Experimental Medicine*, vol. 172, no. 3, pp. 759–765, 1990.

[21] K. Nosaka, T. Miyamoto, T. Sakai, H. Mitsuya, T. Suda, and M. Matsuoka, "Mechanism of hypercalcemia in adult T-cell leukemia: overexpression of receptor activator of nuclear factor κb ligand on adult T-cell leukemia cells," *Blood*, vol. 99, no. 2, pp. 634–640, 2002.

[22] H. Tsuda, T. Sawada, K. M. Sakata, and K. Takatsuki, "Possible mechanisms for the elevation of serum β2-microglobulin levels in adult T-cell leukemia," *International Journal of Hematology*, vol. 55, no. 2, pp. 179–187, 1992.

[23] N. Sadamori, S. Ikeda, K. Yamaguchi et al., "Serum deoxythymidine kinase in adult T-cell leukemia-lymphoma and its related disorders," *Leukemia Research*, vol. 15, no. 2-3, pp. 99–103, 1991.

[24] S. Kamihira, S. Atogami, H. Sohda, S. Momita, Y. Yamada, and M. Tomonaga, "Significance of soluble interleukin-2 receptor levels for evaluation of the progression of adult T-cell leukemia," *Cancer*, vol. 73, no. 11, pp. 2753–2758, 1994.

[25] S. Kamihira, H. Sohda, T. S. Atogami et al., "Phenotypic diversity and prognosis of adult T-cell leukemia," *Leukemia Research*, vol. 16, no. 5, pp. 435–441, 1992.

[26] A. Inagaki, T. Ishida, T. Ishii et al., "Clinical significance of serum Th1-, Th2- and regulatory T cells-associated cytokines

in adult T-cell leukemia/lymphoma: high Interleukin-5 and -10 levels are significant unfavorable prognostic factors," *International Journal of Cancer*, vol. 118, no. 12, pp. 3054–3061, 2006.

[27] T. Ishida, A. Utsunomiya, S. Iida et al., "Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome," *Clinical Cancer Research*, vol. 9, no. 10 I, pp. 3625–3634, 2003.

[28] T. Kohno, Y. Yamada, N. Akamatsu et al., "Possible origin of adult T-cell leukemia/lymphoma cells from human T lymphotropic virus type-1-infected regulatory T cells," *Cancer Science*, vol. 96, no. 8, pp. 527–533, 2005.

[29] Y. Furukawa, J. Fujisawa, M. Osame et al., "Frequent clonal proliferation of human T-cell leukemia virus type 1 (HTLV-1) -infected T cells in HTLV-1-associated myelopathy (HAM-TSP)," *Blood*, vol. 80, no. 4, pp. 1012–1016, 1992.

[30] S. Ikeda, S. Momita, K. I. Kinoshita et al., "Clinical course of human T-lymphotropic virus type I carriers with molecularly detectable monoclonal proliferation of T lymphocytes: defining a low- and high-risk population," *Blood*, vol. 82, no. 7, pp. 2017–2024, 1993.

[31] K. Tsukasaki, O. Hermine, A. Bazarbachi et al., "Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting," *Journal of Clinical Oncology*, vol. 27, no. 3, pp. 453–459, 2009.

[32] M. Shimoyama, "Major prognostic factors of patients with adult T-cell leukemia-lymphoma: a cooperative study," *Leukemia Research*, vol. 15, no. 2-3, pp. 81–90, 1991.

[33] Y. Yamada, Y. Hatta, K. Murata et al., "Deletions of p15 and/or p16 genes as a poor-prognosis factor in adult T- cell leukemia," *Journal of Clinical Oncology*, vol. 15, no. 5, pp. 1778–1785, 1997.

[34] A. Utsunomiya, T. Ishida, A. Inagaki et al., "Clinical significance of a blood eosinophilia in adult T-cell leukemia/lymphoma: a blood eosinophilia is a significant unfavorable prognostic factor," *Leukemia Research*, vol. 31, no. 7, pp. 915–920, 2007.

[35] Y. Takasaki, M. Iwanaga, K. Tsukasaki et al., "Impact of visceral involvements and blood cell count abnormalities on survival in adult T-cell leukemia/lymphoma (ATLL)," *Leukemia Research*, vol. 31, no. 6, pp. 751–757, 2007.

[36] N. Ohno, A. Tani, K. Uozumi et al., "Expression of functional lung resistance-related protein predicts poor outcome in adult T-cell leukemia," *Blood*, vol. 98, no. 4, pp. 1160–1165, 2001.

[37] M. Tawara, S. J. Hogerzeil, Y. Yamada et al., "Impact of p53 aberration on the progression of Adult T-cell Leukemia/Lymphoma," *Cancer Letters*, vol. 234, no. 2, pp. 249–255, 2006.

[38] Y. Takasaki, M. Iwanaga, Y. Imaizumi et al., "Long-term study of indolent adult T-cell leukemia-lymphoma," *Blood*, vol. 115, no. 22, pp. 4337–4343, 2010.

[39] A. Bazarbachi, Y. Plumelle, J. Carlos Ramos et al., "Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes," *Journal of Clinical Oncology*, vol. 28, no. 27, pp. 4177–4183, 2010.

[40] M. Shimoyama, K. Ota, M. Kikuchi et al., "Chemotherapeutic results and prognostic factors of patients with advanced non-Hodgkin's lymphoma treated with VEPA or VEPA-M," *Journal of Clinical Oncology*, vol. 6, no. 1, pp. 128–141, 1988.

[41] M. Shimoyama, K. Ota, M. Kikuchi et al., "Major prognostic factors of adult patients with advanced T-cell lymphoma/leukemia," *Journal of Clinical Oncology*, vol. 6, no. 7, pp. 1088–1097, 1988.

[42] K. Tobinai, M. Shimoyama, K. Minato et al., "Japan Clinical Oncology Group phase II trial of second-generation LSG4 protocol in aggressive T- and B-lymphoma: a new predictive model for T- and B-lymphoma," *Proceedings of American Society of Clinical Oncology*, vol. 13, p. 378, 1994.

[43] K. Tobinai, M. Shimoyama, S. Inoue et al., "Phase I study of YK-176 (2'-deoxycoformycin) in patients with adult T-cell leukemia-lymphoma. The DCF Study Group," *Japanese Journal of Clinical Oncology*, vol. 22, no. 3, pp. 164–171, 1992.

[44] K. Tsukasaki, K. Tobinai, M. Shimoyama et al., "Deoxycoformycin-containing combination chemotherapy for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study (JCOG9109)," *International Journal of Hematology*, vol. 77, no. 2, pp. 164–170, 2003.

[45] Y. Yamada, M. Tomonaga, H. Fukuda et al., "A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukaemia-lymphoma: Japan Clinical Oncology Group Study 9303," *British Journal of Haematology*, vol. 113, no. 2, pp. 375–382, 2001.

[46] K. Tsukasaki, A. Utsunomiya, H. Fukuda et al., "VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group study JCOG9801," *Journal of Clinical Oncology*, vol. 25, no. 34, pp. 5458–5464, 2007.

[47] K. Itoh, T. Ohtsu, H. Fukuda et al., "Randomized phase II study of biweekly CHOP and dose-escalated CHOP with prophylactic use of lenograstim (glycosylated G-CSF) in aggressive non-Hodgkin's lymphoma: Japan clinical oncology group study 9505," *Annals of Oncology*, vol. 13, no. 9, pp. 1347–1355, 2002.

[48] K. Yasuo, H. Shuichi, F. Tatsuhiko et al., "Expression of P-glycoprotein in adult T-cell leukemia cells," *Blood*, vol. 76, no. 10, pp. 2065–2071, 1990.

[49] K. Tsukasaki, S. Ikeda, K. Murata et al., "Characteristics of chemotherapy-induced clinical remission in long survivors with aggressive adult T-cell leukemia/lymphoma," *Leukemia Research*, vol. 17, no. 2, pp. 157–166, 1993.

[50] M. Ichimaru, S. Kamihira, Y. Moriuchi et al., "Clinical study on the effect of natural α-interferon (HLBI) in the treatment of adult T-cell leukemia," *Gan to Kagaku Ryoho*, vol. 15, no. 10, pp. 2975–2981, 1988 (Japanese).

[51] P. S. Gill, W. Harrington, M. H. Kaplan et al., "Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine," *The New England Journal of Medicine*, vol. 332, no. 26, pp. 1744–1748, 1995.

[52] O. Hermine, D. Bouscary, A. Gessain et al., "Brief report: treatment of adult T-cell leukemia-lymphoma with zidovudine and interferon alfa," *The New England Journal of Medicine*, vol. 332, no. 26, pp. 1749–1751, 1995.

[53] K. Tobinai, Y. Kobayashi, M. Shimoyama et al., "Interferon alfa and zidovudine in adult T-cell leukemia-lymphoma," *The New England Journal of Medicine*, vol. 333, no. 19, pp. 1285–1286, 1995.

[54] J. D. White, G. Wharfe, D. M. Stewart et al., "The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma," *Leukemia and Lymphoma*, vol. 40, no. 3-4, pp. 287–294, 2001.

[55] E. Matutes, G. P. Taylor, J. Cavenagh et al., "Interferon α and zidovudine therapy in adult T-cell leukaemia lymphoma: