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Review Article: Study Group

Lymphoma Study Group of JCOG

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The Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) was initiated in 1978 by five institutions and now has 47 members. JCOG-LSG has focused on combined modalities, dose intensification and the incorporation of new agents for major disease entities of lymphoid malignancies. More than 30 trials including 10 randomized trials have been conducted for aggressive non-Hodgkin's lymphoma (NHL), adult T-cell leukemia–lymphoma (ATL), lymphoblastic lymphoma/acute lymphoblastic leukemia, Hodgkin's lymphoma (HL), multiple myeloma, NK/T-NHL and indolent B-NHL, and correlative epidemiological and pathological studies have been performed on human T-lymphotropic virus type-I and T/B cell phenotypes. The first trials for aggressive NHL revealed significant differences in the prognosis of ATL, non-ATL T-NHLs and B-NHLs, establishing a subclassification of ATL, and leading to the establishment of standard therapies for ATL and localized nasal natural killer/T-NHL. Recently, for B-NHLs including diffuse large B-cell lymphoma, mantle cell lymphoma, and indolent B-NHLs, regimens incorporating rituximab have been evaluated. The JCOG-LSG trials for HL led to the approval of dacarbazine for the National Health Insurance in Japan. The multicenter trials by the JCOG-LSG combining new modalities such as molecular-targeting agents will contribute to further improvements in the treatment of lymphoid malignancies.

Key words: clinical trial – lymphoid malignancy – Lymphoma Study Group – Japan Clinical Oncology Group – T- and B-cell lymphoma

INTRODUCTION

Lymphoid malignancies consist of B-cell and T/natural killer (NK)-cell neoplasms, which are clonal tumors of mature and immature B cells, T cells or NK cells at various stages of differentiation (1). Paradigm shifts in the management of lymphoid malignancies have been achieved by the discovery of new disease entities, revision of classifications and development of new agents. The diagnosis of lymphoid malignancies improved significantly in the 1980s mainly with the development of immunophenotypic analyses using monoclonal antibodies. This resulted in the discovery of several new disease entities. Among them, adult T-cell leukemia–lymphoma (ATL) was first described in Japan by Takatsuki and colleagues (2) in 1977 and was found to be associated with human T-lymphotropic virus type-I (HTLV-1), the first RNA retrovirus associated with human diseases, in the early 1980s (3–5).

Treatment of lymphoid malignancies has been improved by the development of standard combination chemotherapy such as CHOP, secondary in association with the advances in diagnosis and classification described above, and by the development of new agents and modalities such as an anti-CD20 antibody for CD20-expressing B cell

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

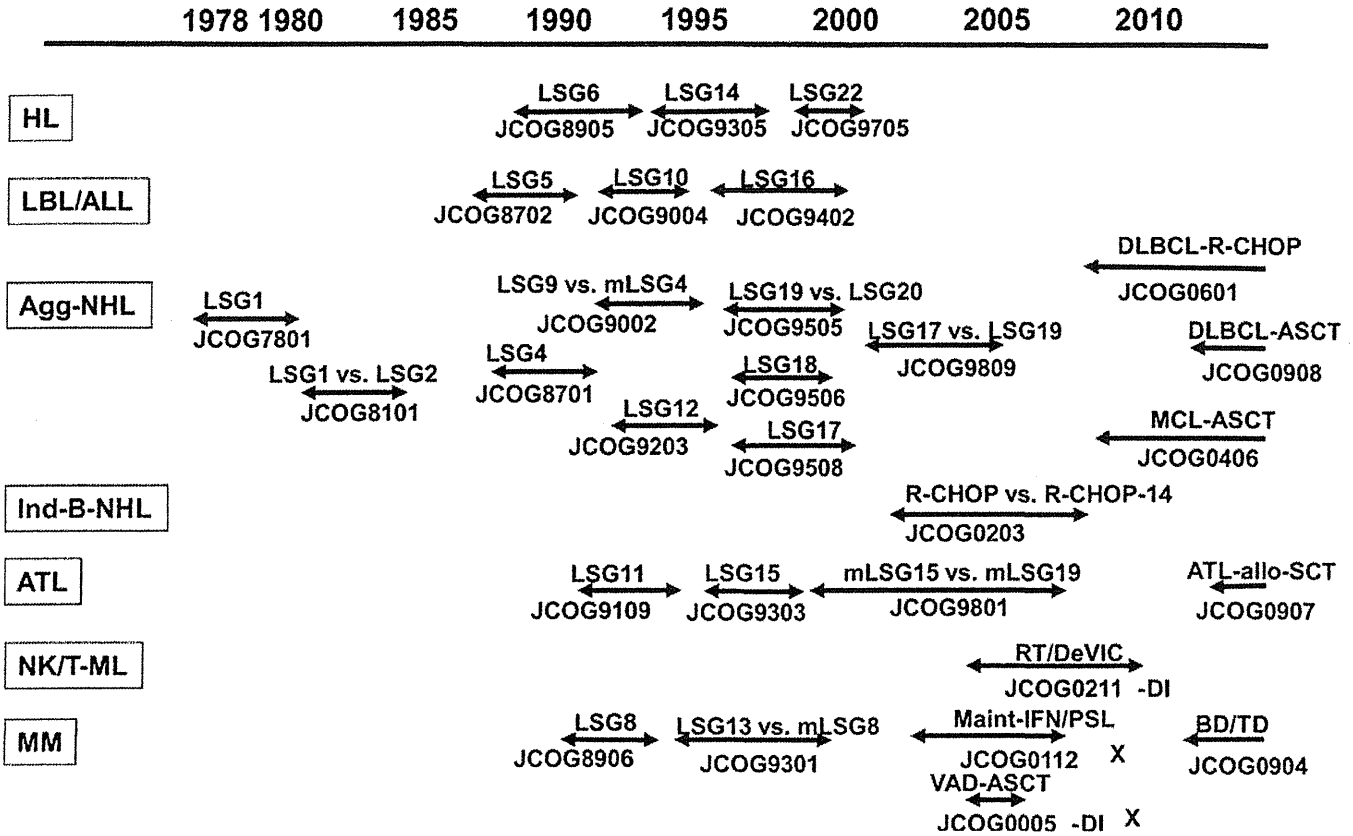

Figure 1. Consecutive studies by JCOG-LSG. HL, Hodgkin's lymphoma; LBL/ALL, lymphoblastic lymphoma/acute lymphoblastic leukemia; Agg-NHL, aggressive non-Hodgkin's lymphoma; Ind-B-NHL, indolent B-NHL, ATL; adult T-cell leukemia–lymphoma; NK/T ML, localized nasal natural killer/T-cell lymphoma; MM, multiple 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.

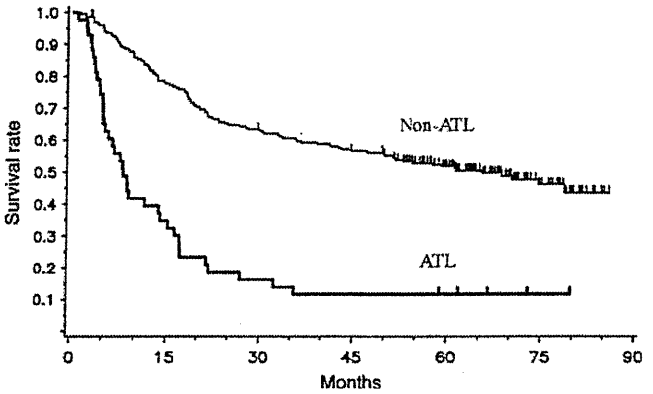

Figure 2. The Kaplan–Meier estimate of overall survival for all patients treated with LSG4 in relation to disease entity. ATL, adult T-cell leukemia–lymphoma.

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.

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Guest editorial: Management of malignant lymphoma is continuously improving

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This issue of IJH contains four "Progress in Hematology (PIH)" review articles describing the management of malignant lymphoma, with a focus on recent clinical trials. Malignant lymphoma, characterized by its marked heterogeneity, is the most frequent hematologic malignancy in the world. Among the various subtypes of malignant lymphoma, the following three are clinically important: Hodgkin lymphoma, follicular lymphoma (FL), and diffuse large B cell lymphoma (DLBCL). The current and future management of these three major subtypes are discussed by internationally distinguished lymphoma experts who have contributed to the establishment of the current standard management of each subtype. In addition, the current and future management of NK/T cell lymphoma is discussed by Dr. Yamaguchi, based on clinical trials recently published by her group.

Current issues to be addressed in the management of malignant lymphoma differ somewhat from disease to disease. In Hodgkin lymphoma, continuous efforts to establish more effective chemotherapy with or without radiotherapy have yielded high cure rates in patients with localized and advanced diseases. Drs. Eichenauer and Engert of the German Hodgkin Study Group (GHSG) prepared a comprehensive review article regarding the current standard management, based mainly on clinical trials conducted by GHSG. Treatment strategies for Hodgkin lymphoma are scientifically discussed, and updated information, including that on ongoing clinical trials, should help readers to better understand the most successful history of using non-surgical treatment modalities in clinical oncology.

In FL, which remains incurable in most patients, the issues are somewhat different from those in Hodgkin lymphoma. Anti-CD20 monoclonal antibodies, such as rituximab, and radioimmunotherapy have markedly prolonged survival. In the second PIH article, Drs. Salles and Ghesquières of Groupe d'Etudes des Lymphomes de l'Adulte (GELA), which has recently been renamed the Lymphoma Study Association (LYSA), summarize recent advances in the management of patients with FL, based on the results of recent clinical trials including the PRIMA Study, which revealed the efficacy of maintenance use of rituximab [1]. Considering the marked heterogeneity of FL, the prolonged median survival time probably exceeding 15 years under the current treatment modalities, and the emergence of several less toxic but highly effective agents, personalized approaches will be more important in the treatment of FL in the future.

Since the establishment of rituximab plus CHOP as a standard therapy for DLBCL [2], progress has been less remarkable. In the third PIH article in this issue, Drs. Roschewski, Dunleavy, and Wilson of the National Cancer Institute in the United States present an excellent review of further progress in the treatment of DLBCL. An improved understanding of the biology of DLBCL has revealed a number of oncogenic driver mutations and signaling pathways essential for growth of the lymphoma cell. As many of these signaling pathways can be targeted by small molecule inhibitors, treatment of DLBCL may be in store for a paradigm shift.

Finally, Dr. Yamaguchi in Japan summarizes newly developed treatment strategies for NK/T cell lymphoma, based on the results of multicenter clinical trials. NK/T cell lymphoma is a distinct disease subtype with dismal prognosis

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when treated by conventional methods [3]. NK/T cell lymphoma is quite rare in Western countries, but relatively more common in East Asian countries, raising expectations that Asian investigators will contribute to the establishment of therapeutic advances. Recently, Dr. Yamaguchi and her colleagues published the results of prospective clinical trials of concurrent chemoradiotherapy for localized disease in the nasopharynx [4] and a novel combination chemotherapy regimen for advanced disease [5].

I am confident that all of the review articles in this issue of IJH will provide readers with the most up to date information on the current standard management for major subtypes of malignant lymphoma, and new insights into future directions in the management of the most frequent hematologic malignancy in the world.

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Phase II Study of Intensive Post-remission Chemotherapy and Stem Cell Transplantation for Adult Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma: Japan Clinical Oncology Group Study, JCOG9402

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Objective: To evaluate the efficacy and safety of intensive post-remission chemotherapy for untreated patients aged 15–69 years with adult acute lymphoblastic leukemia and lymphoblastic lymphoma in a multicenter Phase II study.
Methods: The chemotherapy regimen consisted of induction, post-remission and maintenance for 2 years. The primary endpoint was 5-year progression-free survival, and secondary endpoints included complete remission rate, overall survival and adverse events. Among 115 patients enrolled, 108 eligible patients [median age, 33.5 years (range, 15–69)] including 96 acute lymphoblastic leukemia and 12 lymphoblastic lymphoma were assessed. Other major characteristics were male 50%, T-cell phenotype 21%, Philadelphia chromosome 22%, B-symptom+ 35% and performance status 2/3 22%.
Results: Eighty-seven patients achieved complete remission (81%; 95% confidence interval 72–88%), while five (5%) died during the chemotherapy protocol. The median overall survival and progression-free survival were 1.8 years (95% confidence interval, 1.5–2.6) and 1.2 years (95% confidence interval, 0.8–1.6), respectively. Their 5-year overall survival and progression-free survival were 29 and 28%, respectively. The 5-year overall survival of 31 patients who underwent allogeneic ($n = 19$) or autologous ($n = 12$) stem cell transplantation during first complete response was 51%. Major non-hematologic toxicities of Grade 3 or greater were infections (21%) and pulmonary complications (6%). When compared with the investigators' previous Phase II trials, JCOG9402 improved progression-free survival and overall survival when compared with JCOG8702; however, it did not show improvement when compared with JCOG9004.

Conclusions: Although the intensified induction and post-remission chemotherapy was feasible and 28% of the patients with adult acute lymphoblastic leukemia or lymphoblastic lymphoma achieved long-term progression-free survival, JCOG9402 did not show improvement.

Key words: chemo-haematopoietic – clinical trials – hematol-leukemia/lymphoma – hematol-transplantation

INTRODUCTION

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are categorized as precursor B- or T-cell malignancy (1) and show overlapping clinical features, including leukemic manifestation and a high prevalence of central nervous system (CNS) involvement. ALL and LBL of the T-cell phenotype are frequently accompanied by a mediastinal mass (1,2). Within each cell lineage, there is clinical and biological overlap between ALL and LBL. Based on these aspects, patients with ALL and those with LBL have been treated with similar chemotherapy regimens (3–7). Generally, however, the prognosis of adult patients is unfavorable compared with pediatric patients (3–11).

Previously, the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) conducted two Phase II studies against ALL and LBL, JCOG8702 and JCOG9004 (12,13). JCOG8702 was designed to improve the therapeutic results of adult ALL and LBL, using VEPA [vincristine (VCR), cyclophosphamide (CPA), prednisolone (PSL) and doxorubicin (DXR)], L-asparaginase (L-asp) and intermediate-dose methotrexate (MTX) without maintenance therapy with oral 6-mercaptopurine (6-MP) and MTX. Although JCOG8702 showed a satisfactory complete remission (CR) rate (%CR) (78%, 36/46), the long-term survival [7-year overall survival (OS), 15%] was inferior to that of the published programs incorporating maintenance therapy (12). The investigators concluded that simplified JCOG8702 therapy without maintenance therapy does not deserve further investigation.

Subsequently, JCOG9004 was designed to mainly evaluate intensive post-remission therapy. The following three strategies were undertaken: (i) intensive post-remission therapy with the prophylactic use of granulocyte colony-stimulating factor (G-CSF); (ii) long-term maintenance therapy including 6-MP and MTX; and (iii) allogeneic and autologous stem cell transplantation (SCT).

Various strategies have been evaluated in the treatment of adult ALL. The Japan Adult Leukemia Study Group (JALSG) evaluated a response-oriented individualized induction therapy in their ALL87 and ALL90 studies (14,15) and intensified induction and consolidation therapy by dose intensification of DXR in their ALL93 and ALL97 studies (16,17), respectively; however, the advantage of these treatment strategies remain unclear. In the early 1990s, especially at the time of designing this study, the significance of post-remission therapy on the outcome of ALL patients had been recognized (3). In particular, autologous and allogeneic SCT had been thought to be promising (18).

Based on these findings, we planned to conduct this multicenter Phase II study, JCOG9402, to further improve the outcome of adult patients with ALL and LBL by the following strategies: (i) consolidation including cytosine arabinoside (Ara-C); (ii) prophylactic intrathecal MTX (IT-MTX) eight times to prevent a CNS relapse; (iii) interim maintenance with MTX and 6-MP; (iv) intensification consisting of DXR, VCR, PSL, CPA, Ara-C and 6-MP; (v) maintenance consisting of vindesine (VDS), CPA, DXR, PSL, 6-MP and MTX for 60 weeks; (vi) allogeneic SCT in first CR; and (vii) autologous SCT in LBL patients. We evaluated the efficacy and safety of this sequential chemotherapy for untreated adult patients with ALL and LBL, focusing on the long-term follow-up results. The feasibility and efficacy of autologous and allogeneic SCT were also assessed.

PATIENTS AND METHODS

Patients

Patients aged 15–69 years were eligible. ALL and LBL were diagnosed according to the French-American-British (FAB) Classification (19,20) and Working Formulation (21), respectively. Patients with LBL at any stage were eligible. Patients having the following disorders were ineligible: preceding myelodysplastic syndrome, performance status (PS) 4 according to the Eastern Cooperative Oncology Group (ECOG) scale (22), liver dysfunction (liver cirrhosis, total bilirubin $\geq$2.0 mg/dl or hepatic transaminase $\geq 4\times$ upper normal limits), renal dysfunction (serum creatinine $\geq$2.0 mg/dl), hypoxemia ($PaO_2 < 60$ mmHg), diabetes mellitus requiring insulin treatment, severe infection, active tuberculosis, cardiac failure, ischemic heart disease, cardiomyopathy, active concurrent cancer, human immunodeficiency virus infection, severe psychiatric disorder, pregnancy or other severe complications. Patients who had received anticancer agents until enrollment were ineligible, but those receiving radiation or glucocorticoids were eligible.

Immunophenotyping for tumor cells was performed at each institution to distinguish B-cell or T-cell origin. Flow

cytometric analysis was conducted on suspended cells. Samples were judged positive if more than 20% of cells showed specific labeling above those of controls. For biopsied lymph node or tumor samples, immunohistochemical analysis was conducted. Even if the biopsied specimen showed histopathologic findings consistent with LBL, patients having 25% tumor cells or more in their bone marrow (BM) were diagnosed as having ALL (2). It was recommended that a pre-treatment peripheral blood (PB), BM or biopsied specimen be subjected to cytogenetic analysis. Biopsy specimens of patients diagnosed with LBL at each institution were submitted to central pathology review. The data of flow cytometric analyses conducted at each institution were utilized in the central pathology review.

Registration was done by a telephone call or fax from participating physicians to the JCOG Statistical or Data Center (1994–97: Statistical Center; 1998–: Data Center) (23). When a patient achieving first CR met the following eligibility criteria for SCT, the physician was requested to register. For allogeneic SCT, patients had to meet the following criteria: (i) age 15–49 years; (ii) human leukocyte antigen (HLA)-matched sibling donor; (iii) continuous CR after consolidation A; (iv) PS of 0 or 1; (v) $PaO_2 \geq 70$ mmHg; (vi) cardiac ejection fraction $\geq 50\%$; (vii) creatinine clearance ≥ 50 ml/min; (viii) written informed consent from each patient and his/her donor. For autologous SCT, patients should meet the following criteria: (i) histopathologic LBL; (ii) no matched sibling donor; (iii) no tumor cells in BM or PB at stem cell harvest, in addition to the above-described criteria (i) and (iii)–(vii) for allogeneic SCT.

The study protocol was approved by the Protocol Review Committee of the JCOG and by the institutional review board at each institution. Before treatment, informed consent was obtained from each patient or his/her family member.

Treatments

Chemotherapy

The total treatment plan is shown in Fig. 1, and drug doses and administration schedules are listed in Table 1. The treatment regimens consisted of one cycle of induction, one cycle of consolidation A and consolidation B, CNS prophylaxis, interim maintenance, intensification and five cycles of maintenance. During and after administration of L-asp in induction therapy, it was recommended that fresh-frozen plasma or anti-thrombin be given to patients showing a marked decrease in fibrinogen and anti-thrombin III. The total planned duration of treatment was 102 weeks. For patients who did not achieve CR with induction therapy, consolidation A and consolidation B were given. For those who did not achieve CR by then, protocol treatment was terminated. Testicular irradiation or CNS irradiation was not administered prophylactically, but irradiation of a mass lesion initially presenting as over 5 cm in diameter was recommended after consolidation therapy. Because severe complications such as pancreatitis and hyperglycemia occurred, L-asp was withdrawn from consolidation B according to the recommendation of the JCOG Data and Safety Monitoring Committee in September 1996.

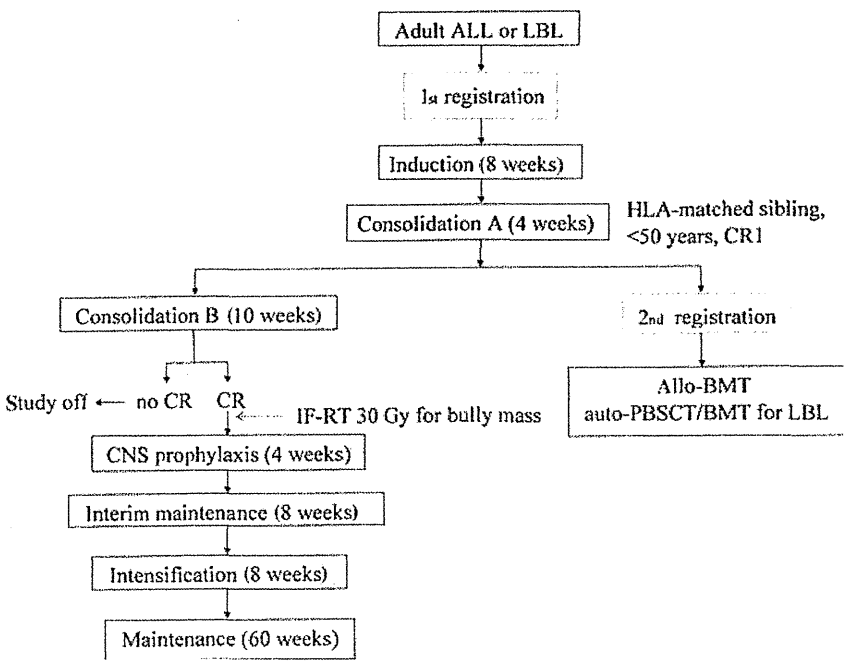

Figure 1. Total treatment scheme of the JCOG9402 protocol. ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma; HLA, human leukocyte antigen; CR, complete remission; IF-RT, involved-field radiotherapy; CNS, central nervous system; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation.

Table 1. Drug doses and administration schedules in JCOG9402

Agent	Route	Dose (≥60 years old)	Schedule (≥60 years old)
Induction			
Vincristine	IV	1.4 mg/m^2 up to 2.0 mg total	Days 1, 8, 15, 22, 29
Cyclophosphamide	IV	600 mg/m^2 (400 mg/m^2)	Days 1, 15, 29
Prednisolone	PO	40 mg/m^2	Days 1–28, then taper (days 1–7, no taper)[a]
Doxorubicin	IV	40 mg/m^2 (30 mg/m^2)	Days 1, 8, 22
L-Asparaginase	IV	6000 U/m^2 (4000 U/m^2)	Days 22–28
Methotrexate	IT	15 mg/patient	Day 15
Prednisolone	IT	20 mg/patient	Day 15
Consolidation A			
Daunorubicin	IV	40 mg/m^2 (30 mg/m^2)	Days 1, 2
Cytosine arabinoside	CI	75 mg/m^2	Days 1–7
Vindesine	IV	2.4 mg/m^2 (2.0 mg/m^2)	Day 1
Prednisolone	PO	40 mg/m^2	Days 1–7, no taper
Methotrexate	IT	15 mg/patient	Day 1
Prednisolone	IT	20 mg/patient	Day 1
Consolidation B			
Cyclophosphamide	IV	1000 mg/m^2 (700 mg/m^2)	Days 1, 29
Cytosine arabinoside	CI	75 mg/m^2	Days 1–7, 29–35
6-Mercaptopurine	PO	60 mg/m^2	Days 1–7, 29–35 (no allopurinol)
Vincristine	IV	1.4 mg/m^2 up to 2.0 mg total	Days 15, 22, 43, 50
L-Asparaginase[b]	IM/SQ	6000 U/m^2 (4000 U/m^2)	Days 15, 18, 22, 25, 43, 46, 50, 53
Methotrexate	IT	15 mg/patient	Days 1, 29
Prednisolone	IT	20 mg/patient	Days 1, 29
CNS prophylaxis and interim maintenance			
6-Mercaptopurine	PO	60 mg/m^2	Days 1–70 (no allopurinol)
Methotrexate	PO	20 mg/m^2	Days 29, 36, 43, 50, 57, 64
Methotrexate	IT	15 mg/patient	Days 1, 8, 15, 22
Prednisolone	IT	20 mg/patient	Days 1, 8, 15, 22
Intensification			
Doxorubicin	IV	30 mg/m^2	Days 1, 8, 15
Vincristine	IV	1.4 mg/m^2 up to 2.0 mg total	Days 1, 8, 15
Prednisolone	PO	40 mg/m^2	Days 1–14, then taper (days 1–7, no taper)[a]
Cyclophosphamide	IV	1000 mg/m^2 (700 mg/m^2)	Day 29
Cytosine arabinoside	CI	75 mg/m^2	Days 29–35
6-Mercaptopurine	PO	60 mg/m^2	Days 29–35 (no allopurinol)
Maintenance[c]			
Vindesine	IV	2.4 mg/m^2 (2.0 mg/m^2)	Days 1, 22
Cyclophosphamide	IV	600 mg/m^2 (400 mg/m^2)	Day 1
Prednisolone	PO	40 mg/m^2	Days 1–3, 22–24, no taper
Doxorubicin	IV	40 mg/m^2 (30 mg/m^2)	Day 1
Methotrexate	PO	20 mg/m^2	Days 22, 29, 36, 43, 50, 57

Continued

Table 1. *Continued*

Agent	Route	Dose (≥60 years old)	Schedule (≥60 years old)
6-Mercaptopurine	PO	60 mg/m^2	Days 22–56 (no allopurinol)

The doses and schedules in parentheses indicate those for patients aged 60 years or older.
IV, intravenously; PO, per os (orally); IT, intrathecally; CI, continuous infusion; IM, intramuscullary; SQ, subcutaneously.
[a]Also given to post-menopausal women aged <60 years old.
[b]L-Asparaginase was withdrawn from consolidation B regimen in September 1996 because of severe adverse events including pancreatitis.
[c]This maintenance regimen was repeated at least five cycles every 3 months until 2 years after induction chemotherapy.

Stem cell transplantation

For patients aged 15–49 years with an HLA-matched related donor who achieved CR and met the eligibility criteria for SCT, allogeneic SCT was recommended after consolidation A. For LBL patients aged 15–49 years without HLA-matched sibling donors, non-purged autologous SCT (PB or BM) was recommended. For conditioning before SCT, one of the following regimens was taken: busulfan (1 mg/kg × 4/day orally for 4 days on days −7 to −4) and CPA (60 mg/kg/day on days −3 and −2) (24), or CPA (60 mg/kg/day on consecutive 2 days until day −2) and total body irradiation (TBI; 12 Gy by 4–6 fractions on consecutive 2–3 days until day −1) were given. For prophylaxis of acute graft-versus-host disease, cyclosporine A and short-term MTX were given (25); however, the doses of MTX were reduced to 10 mg/m^2 on day 1 and 7 mg/m^2 on days 3 and 5 (26).

Modification of doses and schedules

For patients aged 60 years or older, the dose reductions and schedule modifications were performed as shown in Table 1. Treatment was postponed if the aspartate aminotransferase (AST) [glutamic oxaloacetic transaminase (GOT)] or alanine aminotransferase (ALT) [glutamic pyruvic transaminase (GPT)] level was over 200 U or if the total bilirubin was over 2.0 mg/dl. DXR or daunorubicin was omitted when cardiotoxicities such as tachycardia, arrhythmia, ejection fraction <40% and cardiomyopathy developed. In patients seropositive for hepatitis B virus surface antigen or hepatitis C virus antibody, PSL was omitted. In patients developing an infection of Grade 3 or greater, treatment was postponed, and the doses of 6-MP and MTX in the interim maintenance therapy were reduced to 50% for <750/mm^3 of neutrophils or <50 000/mm^3 of platelets, or skipped for <500/mm^3 of neutrophils, <30 000/mm^3 of platelets or over three times higher than the upper normal limit of AST or ALT. After recovery of those toxicities, 6-MP and MTX were given again at the 50% dose and increased to the full dose if possible. In patients who developed constipation of Grade 3 or greater caused by vinca alkaloids, their administration was skipped. In patients who developed Grade 4 paralytic ileus, all treatments were discontinued. In patients suffering from VCR-induced neurotoxicity, VCR could be changed to VDS. In those who developed CPA-induced hemorrhagic cystitis, CPA was omitted in subsequent cycles. Hyperglycemia was treated with insulin, but in uncontrollable patients, PSL was reduced in doses or discontinued. In patients with psychosis, osteoporosis or hypertension exaggerated by PSL, PSL was reduced in doses or discontinued. In patients with paralysis, convulsion or psychosis developing 72 h after IT-MTX, it was withdrawn. In patients developing arachnoiditis associated with IT-MTX, it was switched to IT-Ara-C (Ara-C 40 mg + PSL 20 mg).

Supportive therapy

Trimethoprim/sulfamethoxazole was recommended for the prophylaxis of *Pneumocystis jirovecii* pneumonia. G-CSF was prophylactically used when the neutrophil count decreased to <1000/mm^3. Appropriate antibiotics were given for neutropenic infection. When they were not effective, the addition of anti-fungal agents was recommended. The prophylactic use of amphotericin-B syrup for fungal infection of the oral cavity and esophagus was recommended. In patients with suspected varicella zoster virus infection or herpes simplex virus infection, acyclovir was given immediately. Adequate drugs for peptic ulcer were given during PSL administration. Total parenteral nutrition was recommended when patients' intake decreased by chemotherapy. Attention was paid to patients with cough, dyspnea and fever to make early diagnosis of interstitial pneumonia and to start appropriate treatment.

Criteria for Response

Patients with ALL were judged to have achieved CR when the results of a BM examination became normal (blasts ≤5%) along with the normalization of all abnormal laboratory findings such as absolute neutrophil count >1000/mm^3 and platelets >100 000/mm^3, and all extramedullary diseases had resolved. Patients with LBL were judged to have achieved CR when the tumor or swollen lymph nodes disappeared for more than 4 weeks, according to the WHO response criteria (27).

Toxicity

Toxicity was assessed according to the JCOG toxicity criteria, an expanded version of the Common Toxicity Criteria version 1.0 by the National Cancer Institute (28).

Endpoint

The primary endpoint was 5-year progression-free survival (PFS). Secondary endpoints included CR rate (%CR), OS and adverse events.

Statistical Analysis

A required sample size to evaluate chemotherapy was 97 patients with one-sided α of 0.05, β of 0.20, an expected %5-year PFS of 30% and a threshold %5-year PFS rate of 14.3% (29). Considering ineligible patients, a planned sample size was determined as 120. %CR was evaluated in 108 eligible patients. OS and PFS were evaluated in 108 eligible patients, 87 patients who achieved CR, Philadelphia (Ph) chromosome-negative ALL patients (72 patients) and adolescent and young adult (AYA) patients aged 25 years old or younger (41 patients). Survival curves were estimated with the Kaplan–Meier method. The difference between survival curves according to each characteristic was analyzed using the log-rank test. The Cox proportional hazards regression analysis was performed to assess the association between each patient characteristic and OS. All analyses were carried out with SAS release 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Between November 1994 and December 1999, 115 newly diagnosed patients with ALL or LBL aged 15–69 years were registered from 27 institutions, and 108 (94%) were eligible. Case report forms of one patient were lost. Two enrolled patients under the institutional diagnosis of LBL were judged ineligible by the central pathology review, because each diagnosis was changed to Burkitt's lymphoma. The remaining five patients, including one patient who was ineligible by the central pathology review, were ineligible due to the following reasons; a diagnosis of diffuse large B-cell lymphoma, small cell lung cancer and granulocytic sarcoma, prior therapy and coexistence of miliary tuberculosis at enrollment. In five other eligible patients, the clinical diagnosis was changed to ALL because the neoplastic cells in BM were 25% or more (2). The 108 eligible patients ranged in age from 15 to 69 years, with a median of 33.5 years (38.5 years in ALL and 20.5 years in LBL, respectively). Immunophenotypic analysis was adequately performed in 100 (93%) of 108 eligible cases (Table 2). Among those cases, 69 (64%) were categorized as B-lineage, whereas 23 (21%) as T-lineage. Cytogenetic analysis was performed in 96 (89%) of 108 cases. Ph chromosome and t(4;11) were detected in 24 (22%) and 2 (2%) cases, respectively. Other chromosomal abnormalities were reported in 22 cases (20%), normal karyotypes in 32 (30%) and indeterminate results in 16 (15%).

Table 2. Characteristics of 108 eligible patients

	ALL (96)	LBL (12)	Total (*n*, %)
Immunophenotype			
T-lineage	13 (14)	10 (83)	23 (21)
B-lineage	69 (72)	0 (0)	69 (64)
Others	8 (8)	0 (0)	8 (7)
NA	6 (6)	2 (17)	8 (7)
FAB subtype			
L1	23 (24)	NA	23 (21)
L2	69 (72)	NA	69 (64)
L3	4 (4)	NA	4 (4)
Chromosome			
Philadelphia chromosome	24 (25)	0	24 (22)
t(4;11)	2 (2)	0	2 (2)
Other abnormalities	22 (23)	0	22 (20)
Normal	29 (30)	3 (25)	32 (30)
Not evaluable	12 (13)	4 (33)	16 (15)
Not examined	7 (7)	5 (42)	12 (11)
PS			
0	32 (33)	3 (25)	35 (32)
1	46 (48)	3 (25)	49 (45)
2	15 (16)	5 (42)	20 (19)
3	3 (3)	1 (8)	4 (4)
B-symptom			
Absence	58 (60)	10 (83)	68 (63)
Presence	36 (38)	2 (17)	38 (35)
Not available	2 (2)	0	2 (2)

ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma; NA, not applicable; FAB, French–American–British Classification; PS, performance status.

Therapeutic Results

Eighty-seven [81%; 95% confidence interval (CI), 72–88%] of the 108 eligible patients achieved CR. Among those who achieved CR, 31 patients proceeded to SCT. At the time of the last follow-up, 29 patients remained alive without progression. The OS and PFS curves of the 108 eligible patients are shown in Fig. 2. The median PFS and OS of all 108 eligible patients were 14 months (95% CI, 10–19 months) and 21 months (95% CI, 18–31 months), respectively. As shown in Fig. 3, the estimated probability of their 5-year OS and

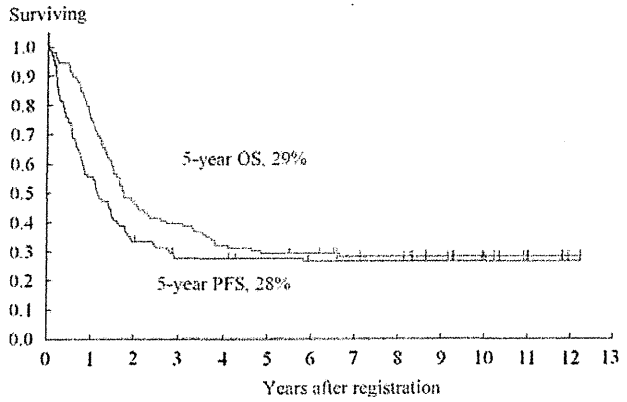

Figure 2. Progression-free survival (PFS) in blue and overall survival (OS) in red of 108 eligible patients with ALL and LBL. The median PFS and OS of the 108 eligible patients were 14 months [95% confidence interval (CI), 10–19 months] and 21 months (95% CI, 18–31 months). Estimated probability of PFS and OS at 5 years were 28% (95% CI, 19–36%) and 29% (95% CI, 21–38%).

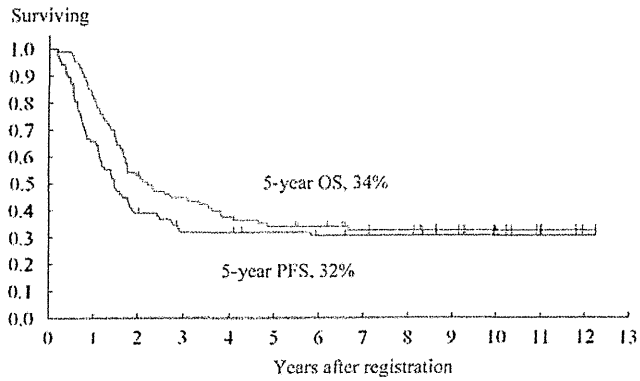

Figure 3. PFS in blue and OS in red of the 87 patients with ALL and LBL who achieved CR. Estimated probability of PFS and OS at 5 years were 32% (95% CI, 22–42%) and 34% (95% CI, 24–44%).

PFS of 87 patients who achieved CR was 34% (95% CI, 24–44%) and 32% (95% CI, 22–42%), respectively.

Eleven patients including one ineligible patient who achieved CR were registered and underwent SCT according to the JCOG9402 protocol, and high-dose busulfan and CPA, or TBI and high-dose CPA as the conditioning regimen; however, several advances in this area during the study period have enabled treating physicians to choose a TBI-based conditioning regimen and an unrelated donor. As a result, 21 patients who achieved CR underwent SCT outside the protocol. To exploratory assess the role of SCT, 31 patients who underwent SCT in the first CR were evaluated separately from the protocol results, as shown in Table 3. Their median age was 24 years. Twenty-four patients (77%) with ALL and seven (23%) with LBL were included. Autologous and allogeneic stem cells were used in 12 (PB in 12 patients) and 19 patients (related donor BM in 11, unrelated donor BM in 6 and related donor PB in 2), respectively. The OS of the 31 patients is shown in Fig. 4, and

Table 3. Characteristics of 31 patients who received stem cell transplantation during first complete remission and main therapeutic results

Patient characteristics	*n*
Registered	10
Not registered	21
Median age (years, range)	24 (16–67)
Gender (male/female)	17/14
Disease	
ALL	24
LBL	7
Chromosome abnormality	
Philadelphia chromosome	3
t(4;11)	0
Conditioning regimen	
BU + CPA	6
CPA + TBI	18
Others	4
Unknown	3
Stem cell source	
Allo-PBSCT	2
Autologous (BM/PB)	0/12
Allogenic (sibling/unrelated)	11/6
Sibling (BM/PB)	11/2
Acute GVHD prophylaxis	
CSP + short-term MTX	15
Others	3
Unknown	1
Results	
Died <100 days after stem cell transplantation	3
5-year overall survival	51% (95% CI, 32–67)
Alive at last follow-up	16

BU, busulfan; CPA, cyclophosphamide; TBI, total body irradiation; PBSCT, peripheral blood stem cell transplantation; BM, bone marrow; PB, peripheral blood; GVHD, graft-versus-host disease; CSP, cyclosporine; MTX, methotrexate; CI, confidence interval.

the estimated probability of OS at 5 years was 51% (95% CI, 32–67%). The estimated survival probabilities of autologous and allogeneic SCT at 5 years were 58% (95% CI, 27–80%) and 47% (95% CI, 24–67%), respectively.

Subgroup analysis

OS was compared between subsets according to the following eight variables: age ($\leq$40 versus >40 years), sex (male versus female), clinical diagnosis (ALL versus LBL), ECOG-PS (0, 1 versus 2–4), leukocytes at initial presentation (<10 000 versus $\geq$10 000/μl), immunophenotype of neoplastic cells (non-T versus T), C-reactive protein