International Journal of Hematology (2018) 107:420–427
https://doi.org/10.1007/s12185-018-2430-6

PROGRESS IN HEMATOLOGY

Current status and progress of lymphoma research in East Asian countries

Epidemiology of malignant lymphoma and recent progress in research on adult T-cell leukemia/lymphoma in Japan

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Received: 13 February 2018 / Revised: 25 February 2018 / Accepted: 25 February 2018 / Published online: 3 March 2018

Abstract
The morbidity and mortality of disease vary according to the region and may also change over time. The morbidity and mortality of malignant lymphoma are also affected by differences in ethnicity, lifestyle habits, geographical area, and time period. Increasing research on malignant lymphoma has focused on its pathophysiology, diagnosis, and therapeutic treatment. Recent improvements in the accuracy of clinical study, technologies such as next-generation sequencing, and the development of targeted molecular agents have also resulted in a number of excellent studies. This review summarizes the epidemiology of malignant lymphoma and highlights novel studies on adult T-cell leukemia/lymphoma recently published in Japan.

Keywords Epidemiology · ATLL · Japan

Epidemiology of malignant lymphoma in Japan

Incidence and mortality rates of malignant lymphoma in Japan

The Center for Cancer Control and Information Services of the National Cancer Center reported estimated malignant lymphoma incidences of 22.3/100,000 and 18.3/100,000 in men and women, respectively, in 2013, with mortality rates of 11.4100,000 and 8.5/100,000 [1]. Worldwide, the incidences of non-Hodgkin lymphoma were 6.0/100,000 and 4.1/100,000 in men and women, with mortalities of 3.2/100,000 and 2.0/100,000, respectively [2]. The number of patients with malignant lymphoma is reportedly increasing worldwide, including Japan, although the rate of increase differs in each country [3].

Proportions of subtypes in Japan

Although B-cell lymphomas tend to account for a large proportion of cases worldwide, the proportion varies depending on the region. The breakdown of subtypes of cases ($N=1442$) diagnosed in Kurume University in Japan in 2014 is shown in Table 1. B-cell neoplasms, T/NK cell neoplasms, and Hodgkin lymphoma were observed in 70.8, 16.4, and 6.4% of the cases, respectively. Diffuse large B-cell lymphoma (DLBCL) occurred in 35.8% of cases, followed by follicular lymphoma (FL, 21.7%), adult T-cell leukemia/lymphoma (ATLL, 5.8%), angioimmunoblastic T-lymphoma (AITL, 4.8%), extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma, 3.4%), mantle cell lymphoma (MCL, 3.3%), peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS, 2.8%), and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (1.7%).

Classification of data from six regions in Japan

To investigate the differences among topographic areas in Japan, Table 2 shows data classified into the Okinawa, Kyushu, Kinki/Chugoku/Shikoku, Chu-bu, Kantou, and Tohoku/Hokkaido regions. Although the proportion of ATLL was higher in Okinawa (16.8%) and Kyushu (9.2%) than those in the other areas, consistent with previous studies

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Table 1 Frequency of subtypes of lymphoid neoplasms stratified by six areas in Japan

	Japan		Okinawa		Kyushu		Kinki/Chu-goku/Shikoku		Chu-bu		Kantou		Tohoku/Hokkaido	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Total cases	1442	100.0	101	100	531	100.0	157	100.0	109	100.0	446	100.0	98	100.0
B-cell neoplasms	1021	70.8	59	58.4	368	69.3	121	77.1	81	74.3	321	72.0	71	72.4
T/NK cell neoplasms	236	16.4	31	30.7	96	18.1	20	12.7	15	13.8	59	13.2	15	15.3
Hodgkin lymphoma	92	6.4	6	5.9	39	7.3	8	5.1	6	5.5	29	6.5	4	4.1
Histiocytic/dendritic cell neoplasms	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0
Composite lymphoma	14	1.0	1	1.0	3	0.6	2	1.3	1	0.9	6	1.3	1	1.0
Immunodeficiency-associated lymphoproliferative disorders	52	3.6	2	2.0	16	3.0	2	1.3	3	2.8	24	5.4	5	5.1
EBV-lymphoproliferative disorder	15	1.0	0	0.0	6	1.1	2	1.3	2	1.8	4	0.9	1	1.0
Other haematopoietic neoplasms	11	0.8	2	2.0	3	0.6	2	1.3	1	0.9	2	0.4	1	1.0
B-cell neoplasms														
Precursor B-lymphoblastic leukemia/lymphoma	4	0.3	1	1.0	1	0.2	1	0.6	0	0.0	1	0.2	0	0.0
Chronic lymphocytic leukemia/small lymphocytic leukemia	15	1.0	2	2.0	6	1.1	0	0.0	3	2.8	3	0.7	1	1.0
Lymphoplasmacytic lymphoma	10	0.7	0	0.0	2	0.4	2	1.3	1	0.9	4	0.9	1	1.0
Mantle cell lymphoma	47	3.3	4	4.0	19	3.6	3	1.9	4	3.7	13	2.9	4	4.1
Follicular lymphoma	313	21.7	16	15.8	118	22.2	32	20.4	26	23.9	93	20.9	28	28.6
Nodal marginal zone B-cell lymphoma	8	0.6	0	0.0	0	0.0	1	0.6	0	0.0	6	1.3	1	1.0
Extranodal marginal zone B-cell lymphoma (MALT)	49	3.4	7	6.9	20	3.8	9	5.7	1	0.9	11	2.5	1	1.0
Splenic marginal zone B-cell lymphoma	4	0.3	0	0.0	1	0.2	0	0.0	0	0.0	3	0.7	0	0.0
Plasma cell neoplasms	5	0.3	0	0.0	2	0.4	1	0.6	0	0.0	2	0.4	0	0.0
Diffuse large B-cell lymphoma	516	35.8	26	25.7	184	34.7	62	39.5	41	37.6	170	38.1	33	33.7
Burkitt lymphoma	9	0.6	0	0.0	4	0.8	1	0.6	2	1.8	2	0.4	0	0.0
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma	25	1.7	2	2.0	8	1.5	6	3.8	3	2.8	4	0.9	2	2.0
T/NK-cell neoplasms														
T-cell prolymphocytic leukemia	2	0.1	0	0.0	0	0.0	0	0.0	1	0.9	1	0.2	0	0.0
Precursor T-lymphoblastic leukemia/lymphoma	7	0.5	0	0.0	4	0.8	1	0.6	1	0.9	1	0.2	0	0.0
Extranodal NK/T-cell lymphoma, nasal type	5	0.3	3	3.0	0	0.0	0	0.0	0	0.0	2	0.4	0	0.0
Mycosis fungoides	2	0.1	1	1.0	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0
Sezary syndrome	1	0.1	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0
Angioimmunoblastic T-lymphoma	69	4.8	2	2.0	23	4.3	4	2.5	6	5.5	26	5.8	8	8.2
Peripheral T-cell lymphoma, not otherwise specified	40	2.8	3	3.0	12	2.3	6	3.8	3	2.8	12	2.7	4	4.1
Adult T-cell leukemia/lymphoma	84	5.8	17	16.8	49	9.2	6	3.8	1	0.9	8	1.8	3	3.1
Anaplastic large cell lymphoma, ALK positive	7	0.5	0	0.0	5	0.9	1	0.6	0	0.0	1	0.2	0	0.0
Anaplastic large cell lymphoma, ALK negative	11	0.8	2	2.0	1	0.2	0	0.0	2	1.8	6	1.3	0	0.0

Table 1 (continued)

	Japan		Okinawa		Kyushu		Kinki/Chu-goku/Shikoku		Chu-bu		Kantou		Tohoku/Hokkaido	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Enteropathy-type-T-cell lymphoma	3	0.2	1	1.0	1	0.2	0	0.0	0	0.0	1	0.2	0	0.0
Hepatosplenic T-cell lymphoma	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	3	0.2	2	2.0	0	0.0	1	0.6	0	0.0	0	0.0	0	0.0
Subcutaneous panniculitis-like T-cell lymphoma	1	0.1	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0
Histiocytic/dendritic cell neoplasms														
Histiocytic sarcoma	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0
Langerhans histiocytosis/sarcoma	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Immunodeficiency-associated lymphoproliferative disorders														
Post-transplant lymphoproliferative disorders	2	0.1	0	0.0	2	0.4	0	0.0	0	0.0	0	0.0	0	0.0
Other iatrogenic immunodeficiency-associated lymphoproliferative disorders	6	0.4	0	0.0	1	0.2	1	0.6	1	0.9	3	0.7	0	0.0
MTX-lymphoproliferative disorders	44	3.1	2	2.0	13	2.4	1	0.6	2	1.8	21	4.7	5	5.1
Other haematopoietic neoplasms														
Granulocytic sarcoma	7	0.5	2	2.0	2	0.4	2	1.3	1	0.9	0	0.0	0	0.0
Blastic plasmacytoid dendritic cell neoplasm	3	0.2	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2	1	1.0

Table 2 Comparison among studies of frequency of lymphoid neoplasm in Japan

	LSG of Japanese Pathologists [5] (1994–1996)	Chihara et al. [6] (1993–2006)	Aoki et al. [4] (2001–2006)	Current study (2014)
Total cases	*N* = 3194	*N* = 26,141	*N* = 2260	*N* = 1442
B-cell neoplasms	68.5%	–	65.2%	70.8%
T/NK cell neoplasms	24.9%	–	25.5%	16.4%
Hodgkin lymphoma	4.4%	–	7.4%	6.4%
Histiocytic/dendritic cell neoplasms	0.3%	–	0.4%	0.1%
B-cell neoplasms				
Precursor B-lymphoblastic leukemia/lymphoma	2.4%	–	0.2%	0.3%
Chronic lymphocytic leukemia/small lymphocytic leukemia	1.3%	2.5	1.4%	1.0%
Lymphoplasmacytic lymphoma	0.7%	–	0.2%	0.7%
Mantle cell lymphoma	2.8%	–	2.7%	3.3%
Follicular lymphoma	6.7%	5.1%	18.3%	21.7%
Nodal marginal zone B-cell lymphoma	1.0%	3.2%	1.4%	0.6%
Extranodal marginal zone B-cell lymphoma (MALT)	8.5%		4.2%	3.4%
Splenic marginal zone B-cell lymphoma	0.1%	–	0.4%	0.3%
Plasma cell neoplasms	9.1%	–	0.6%	0.3%
Diffuse large B-cell lymphoma	33.3%	18.8%	33.1%	35.8%
Burkitt lymphoma	1.0%	–	0.6%	0.6%
T/NK-cell neoplasms				
T-cell prolymphocytic leukemia	0.1%	–	–	0.1%
Precursor T-lymphoblastic leukemia/lymphoma	1.7%	–	0.7%	0.5%
Extranodal NK/T-cell lymphoma, nasal type	2.6%	–	1.6%	0.3%
Mycosis fungoides	1.2%	–	0.5%	0.1%
Sezary syndrome		–		0.1%
Angioimmunoblastic T-lymphoma	2.4%	–	5.1%	4.8%
Peripheral T-cell lymphoma, not otherwise specified	6.7%	3.2%	4.5%	2.8%
Adult T-cell leukemia/lymphoma	7.5%	8.3%	10.0%	5.8%
Anaplastic large cell lymphoma, ALK positive	1.5%	–	0.4%	0.5%
Anaplastic large cell lymphoma, ALK negative		–	1.6%	0.8%
Enteropathy-type-T-cell lymphoma	0.3%	–	0.0%	0.2%
Hepatosplenic T-cell lymphoma	0.1%	–	0.0%	0.0%
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	0.3%	–	–	0.2%
Subcutaneous panniculitis-like T-cell lymphoma	0.1%	–	–	0.1%
Histiocytic/dendritic cell neoplasms				
Histiocytic sarcoma	0.3%	–	0.1%	0.1%
Langerhans histiocytosis/sarcoma		–	0.2%	0.0%

[4, 5], the proportions of the other subtypes did not differ significantly between regions.

Comparison to previous reports in Japan

Table 2 shows comparisons with previous studies in Japan. The Lymphoma Study Group (LSG) of Japanese Pathologists (*N* = 3194; 1994-1996) [5], Chihara et al. (*N* = 26,141; 1993–2006) [6], and Aoki et al. (*N* = 2260; 2001–2006) [4] investigated Japanese data. Although there were few differences among subtypes, the proportions of FL in Aoki et al. (18.3%) and our study (21.7%) were higher than those in the LSG of Japanese Pathologists (6.7%) and Chihara et al. (5.1%). It is possible that temporal changes might have contributed to the higher proportion of FL. Additional studies with larger populations are necessary to investigate this trend because there were also differences in study design among these studies.

Comparison of the proportions of subtypes among China, Korea, and Japan

Comparison of the proportion of subtypes in East Asia, including China [7], Korea [8], and Japan revealed a higher proportion of FL and ATLL cases in Japan and a higher proportion of extranodal NK/T-cell lymphoma, nasal type cases in China (Table 3). Although the results of ATLL and extranodal NK/T-cell lymphoma are compatible to those with previous studies, to our knowledge, the difference in the proportion of FL cases has not been previously reported. The westernization of eating habits may be one of the reasons for this observation.

Recent research on adult T-cell leukemia/lymphoma in Japan

Large retrospective studies of ATLL

Katsuya et al. performed a large retrospective study of 1594 cases of ATLL from 84 institutions, including 895 acute type, 355 lymphoma type, 187 chronic type, and 157 smoldering type according to the Simoyama classification [9]. The median survival times (MSTs) and four-year overall survival (OS) were 8.3 months [95% confidence interval (CI) 7.5–8.9] and 11% for acute type, 10.6 months (95% CI 9.3–11.9) and 11% for lymphoma type, 31.5 months (95% CI 25.9–41.1) and 16% for chronic type, and 55.0 months (95% CI 36.6–90.4) and 52% for smoldering type, respectively.

Previous studies reported that allogeneic hematopoietic stem cell transplantation (allo-HSCT) improved prognosis in cases of acute and lymphoma types [10]. Katsuya et al. also

Table 3 Subtypes of lymphoid neoplasms in China, Korea, and Japan

	Japan		China [7]		Korea [8]	
	N	%	*N*	%	*N*	%
Total cases	1442	100.0	4638	100	5318	100.0
B-cell neoplasms	1021	70.8	2983	64.3	3559	66.9
T/NK cell neoplasms	236	16.4	1082	23.3	667	12.5
Hodgkin lymphoma	92	6.4	399	8.6	219	4.1
B-cell neoplasms						
Precursor B-lymphoblastic leukemia/lymphoma	4	0.3	29	0.6	602	11.3
Chronic lymphocytic leukemia/small lymphocytic leukemia	15	1.0	173	3.7	97	1.8
Lymphoplasmacytic lymphoma	10	0.7	16	0.3	14	0.3
Mantle cell lymphoma	47	3.3	113	2.4	98	1.8
Follicular lymphoma	313	21.7	135	2.9	91	1.7
Nodal marginal zone B-cell lymphoma	8	0.6	9	0.2	54	1.0
Extranodal marginal zone B-cell lymphoma (MALT)	49	3.4	355	7.7	661	12.4
Splenic marginal zone B-cell lymphoma	4	0.3	18	0.4	5	0.1
Diffuse large B-cell lymphoma	516	35.8	1680	36.2	1623	30.5
Burkitt lymphoma	9	0.6	47	1.0	111	2.1
T/NK-cell neoplasms						
T-cell prolymphocytic leukemia	2	0.1	1	0.0	5	0.1
Precursor T-lymphoblastic leukemia/lymphoma	7	0.5	145	3.1	208	3.9
Extranodal NK/T-cell lymphoma, nasal type	5	0.3	509	11.0	206	3.9
Mycosis fungoides	2	0.1	6	0.1	21	0.4
Sezary syndrome	1	0.1				
Angioimmunoblastic T-lymphoma	69	4.8	68	1.5	43	0.8
Peripheral T-cell lymphoma, not otherwise specified	40	2.8	182	3.9	211	4.0
Adult T-cell leukemia/lymphoma	84	5.8	1	0.0	1	0.0
Anaplastic large cell lymphoma, ALK positive	7	0.5	111	2.4	104	2.0
Anaplastic large cell lymphoma, ALK negative	11	0.8				
Enteropathy-type-T-cell lymphoma	3	0.2	8	0.2	17	0.3
Hepatosplenic T-cell lymphoma	0	0.0	16	0.3	3	0.1
Subcutaneous panniculitis-like T-cell lymphoma	1	0.1	29	0.6	17	0.3

observed that cases receiving allo-HSCT had an increased four-year OS of 26%. However, they also reported the significant effect of disease status at the time of allo-HSCT. Although the MSTs from transplantation are 22 months in cases with a first remission, in cases with primary refractory and relapse, the MSTs are only 3 months.

For favorable chronic and smoldering types, the MSTs and four-year OS were not reached (95% CI, 40.7 to not estimable) and 60% and 55.0 months (95% CI 36.6–90.4) and 52%, respectively. The MSTs and four-year OS for the unfavorable chronic type were 27.0 months (95% CI 20.4–35.0) and 29%. The median times from diagnosis to the first-line systemic chemotherapy were also shorter in the unfavorable chronic type (3.7 months, 95% CI 1.4–7.3) than in favorable chronic type (39.1 months (95% CI, 21.8 to not estimable) and smoldering type (56.0 months, 95% CI, 26.1 to not estimable).

Prognostic significance of soluble interleukin-2R in indolent ATLL

Katsuya et al. also investigated the prognostic factors of indolent ATLL in a retrospective study including 149 cases of chronic type and 118 cases of smoldering type ATLL [11]. Soluble interleukin-2 receptor (sIL-2R) was shown to be an independent prognostic factor among clinical features, including Shimoyama's classification [12]. Based on the sIL-2R values, cases of indolent ATLL could be classified in low (sIL-2R < 1000 U/mL), intermediate (1000- < sIL-2R < 6000 U/mL), and high risk (sIL-2R- > 6000 U/mL). The MSTs and 4-year OS were not reached (95% CI 4.6-) and were 77.6% and 5.5 years (95% CI 3.1-), 54.1%, and 1.4 years (95% CI, 0.7–2.6) and 22.1% for low, intermediate, and high-risk, respectively ($P < 0.0001$).

This prognostic classification by sIL-2R can be also adapted as a prediction model for disease progression because the median times to systemic chemotherapy were 8.4, 2.7, and 0.1 years, respectively ($P < 0.0001$). Moreover, this model can statistically stratify cases of indolent ATLL for OS and median times to systemic chemotherapy more appropriately than Shimoyama's classification based on favorable chronic, unfavorable chronic, and smoldering types. Thus, SIL-2R is expected to be used as a prognostic factor of indolent ATLL.

Genomic alterations associated with prognosis in aggressive and indolent ATLL

Based on the research from Katsuya et al. assessing clinical feature as a prognostic factor, Kataoka et al. evaluated 463 cases of ATLL to investigate the associations between genomic alterations and ATLL prognosis [13]. In 97% of cases, one or more somatic alterations, including those on phospholipase C, gamma 1 (*PLCG1*); protein kinase C beta (*PRKCB*); C–C chemokine receptor type 4 (*CCR4*); caspase recruitment domain-containing protein 11 (*CARD11*); signal transducer and activator of transcription 3 (*STAT3*), *VAV1*; tumor protein P53 (*TP53*); and transducin beta like 1 X-linked receptor 1 (*TBL1XR1*), were identified. The genetic profiles differed between aggressive type and indolent type. In comparison to the indolent type, the aggressive type showed an increased association with higher numbers of mutations, focal amplifications and deletions, hyperploid status, and cytosine–guanine dinucleotide island hypermethylation. Mutations in seven genes including *PRKCB, TP53,* interferon regulatory factor 4 (*IRF4*), interferon regulatory factor 2 binding protein 2 (*IRF2BP2*), tet methylcytosine dioxygenase 2 (*TET2*), *CD58*, and beta-2-microglobulin (*B2M)* and focal copy number alterations (CNAs) were more commonly detected in aggressive type than in indolent type. Among the genomic alterations, *IRF4* and *STAT3* mutations were the most significant in aggressive and indolent types, respectively.

Kataoka et al. then proposed a prognostic model that included both genetic abnormality and clinical features. In aggressive type ATLL, *PRKCB* mutations and *PD-L1* amplifications were independent prognostic factors for poor OS as well as Japan Clinical Oncology Group Prognostic Index (JCOG-PI) high-risk categorization and older age (70 years or more). Cases of aggressive type were categorized into three groups according to the number of factors comprising age (70 years or more), *PRKCB* mutations, and *PD-L1* amplifications. There was a significant difference in one-year OS rates among the three groups, with rates of 58% for cases with no risk factors, 45% for those with one risk factor, and 16% for those with two or more risk factors ($P < 0.001$). In indolent type ATLL, *IRF4* mutations, *PD-L1* amplifications, and *CDKN2A* deletions were independent prognostic factors for poor OS and the unfavorable chronic subtype in Shimoyama's classification was not significant. Cases of indolent type were categorized into two groups depending on the presence or absence of at least one factor among *IRF4* mutations, *PD-L1* amplifications, and *CDKN2A* deletions. There was a significant difference in three-year OS rates between the group including cases with no risk factors (82%) and those with at least one risk factor (30%) ($P < 0.001$).

This prognostic model is outstanding because it considers both clinical features and genetic abnormalities of the aggressive and indolent types. This model might be adopted in clinical practice for ATLL.

Biological significance of RHOA mutations in *ATLL*

RHOA mutations are commonly observed in angioimmunoblastic T-cell lymphoma (AITL) [14]. Nagata et al. investigated *RHOA* mutations in 203 cases of ATLL [15]. Although

AITL cases with *RHOA* mutations always have *TET2* mutations [14], *TET2* mutations were less often detected (17%) in *RHOA*-mutated cases of ATLL. The *RHOA* mutations in ATLL showed various patterns of distribution in the GTP-binding pocket. Although the primary mutation in AITL is Gly17Val [14], the mutation hotspots in ATLL include those at the Cys16, Gly17, and Ala161 residues, among which Cys16Arg mutations were most frequent. Although the Gly-17Val mutant in AITL showed little binding to GTP [14], mutants in ATLL bound to GTP more immediately than did wild-type (WT) *RHOA*. The disconnection of GTP and GDP was highly promoted in the ATLL mutants. These results suggest that *RHOA* mutations in ATLL could increase the GDP/GTP exchange rate.

Flow cytometric analyses of ATLL cells with various *RHOA* mutations were performed to investigate whether differences in *RHOA* mutations affected the cell of origin of neoplastic cells. ATLL cells with WT *RHOA*, Cys16Arg, Cys16Gly, and Ala161Pro mutations were likely to be regulatory T-cells or effector T-cells due to their CD4(+), CD25(+), FoxP3(+), PD-1(−) or CD4(+), CD25(+), FOXP3(−), PD-1(−) phenotypes. On the other hand, ATLL cells with Gly17Val were considered to be memory T-cells because of their CD4(+) CD25(-) phenotypes.

Therapeutic effects of lenalidomide in ATLL

Although systemic intensive chemotherapy has been administered for the treatment of ATLL [16], satisfactory effects have not been achieved, especially in aggressive ATLL. Ishida et al. performed a multicenter Phase II study in which lenalidomide was administered for relapsed or recurrent cases of ATLL [17]. An overall response rate of 42% was achieved, including 15% of cases with complete remission (CR), 4% unconfirmed complete remission (CRu), and 23% partial remission (PR). The ORRs were 33% cases of acute type, 57% in lymphoma type, and 50% in unfavorable chronic type. The median time to response, median time to progression, mean duration of response, median progression-free survival, and median OS were 1.9, 3.8, 5.2, 3.8, and 20.3 months, respectively. As described above, the administration of lenalidomide showed a favorable therapeutic effect for relapsed or recurrent cases of ATLL. Lenalidomide might be a possible future option for the treatment of ATLL.

Novel molecular agents in ATLL

Although various therapeutic approaches, including conventional chemotherapy, molecular-targeted agents, anti-viral drugs, and allo-HSCT have gradually improved the prognosis of ATLL, new developments are also underway. Narita et al. reported that BAY1143572, a selective inhibitor of cyclin-dependent kinase 9 (CDK9), could be an effective drug for ATLL following examination of cell lines, ATLL cells from patients, and a mouse model [18]. BAY1143572 suppressed the proliferation in a concentration-dependent manner and induced apoptosis of ATLL-derived or human T-lymphotropic virus type 1 (HTLV-1)-transformed cell lines and ATLL cells from patients by inhibiting the phosphorylation of the Ser2 site in RNAPII. The expressions of the c-Myc and Mcl-1 proteins were also down-regulated. BAY1143572 did not affect the protein expression of HTLV-1 tax and induced various changes in protein expression of HTLV-1 basic leucine zipper (HBZ). The administration of BAY1143572 after injection of ATLL cells in mice caused the suppression of tumor development, decreased liver and bone marrow tumors, reduced sIL-2R levels, and significantly prolonged OS.

Immune checkpoints in ATLL

The biological and clinical significance of tumor immunity has recently been confirmed in hematological malignancy [19] as well as in solid tumor [20, 21]. The importance of programmed cell death ligand 1 (PD-L1) has been reported in ATLL [22]. The reported cases of ATLL included those with PD-L1 expression in neoplastic cells (nPD-L1 + ATLL), those with PD-L1 expression in stromal cells (miPD-L1 + ATLL), and those without PD-L1 expression (PD-L1 − ATLL) (Fig. 1). nPD-L1 + ATLL (MST = 7.5 months) had inferior OS compared to that of nPD-L1 − ATLL (MST = 14.5 months) ($P = 0.0085$). Among nPD-L1 − ATLL, miPD-L1 + ATLL (MST = 18.6 months) showed superior OS compared with that of PD-L1 − ATLL (MST = 10.2 months) ($P = 0.0029$). The expression of nPD-L1 and miPD-L1 maintained its prognostic value for OS

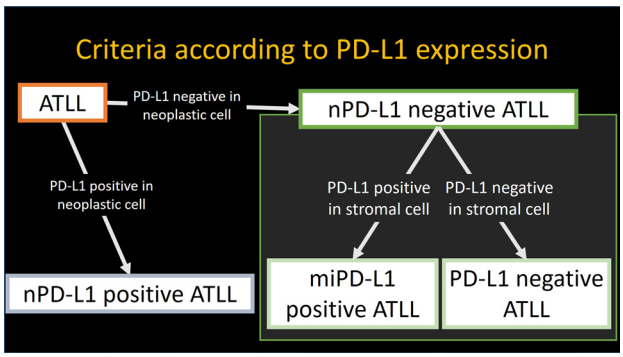

Fig. 1 Criteria according to PD-L1 expression in ATLL. If PD-L1 was expressed on neoplastic cells, the case was categorized as nPD-L1-positive ATLL. If PD-L1 was not expressed on neoplastic cells, the case was considered nPD-L1-negative ATLL. Among nPD-L1-negative ATLL, if stromal cells showed PD-L1 expression, the case was considered miPD-L1-positive ATLL. If the stromal cells did not express PD-L1, the case was considered PD-L1-negative ATLL

in multivariate analysis ($P=0.0322$ and $P=0.0014$, respectively). In nPD-L1 + ATLL, the PD-1/PD-L1 pathway may contribute to a worse prognosis as well as other malignancies. Blockade therapy of the PD-1/PD-L1 pathway might improve the prognosis of nPD-L1 + ATLL. However, in miPD-L1 + ATLL, viral infection including HTLV-1 can induce PD-L1 expression in stromal cells. The reason why miPD-L1 + ATLL shows a better prognosis is unknown; however, the PD-1/PD-L1 pathway might also function in miPD-L1 + ATLL. If the effector function works more in miPD-L1 + ATLL, blockade therapy may result in much better prognosis. The membranous expression of HLA and β2M in ATLL is also associated with better prognosis and might reflect the immune response [23]. The immune checkpoints could be closely associated with ATLL pathogenesis and progression.

Compliance with ethical standards

Conflict of interest There is no conflict of interest to be declared in this review.

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