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Review Article

Clinical management for other iatrogenic immunodeficiency-associated lymphoproliferative disorders

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Other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPD), a category of immunodeficiency-associated LPD according to the World Health Organization classification, is associated with immunosuppressive drugs (ISDs). Several factors, including autoimmune disease (AID) activity, Epstein-Barr virus (EBV) infection, ISD usage, and aging, influence the development of OIIA-LPD, resulting in complicated clinical courses and outcomes. Most OIIA-LPD develops in patients with rheumatoid arthritis using methotrexate (MTX-LPD). The management of MTX-LPD is based on the clinical course, i.e., with/without regression, with/without relapse/regrowth event (RRE), LPD subtype, and ISDs for AIDs after LPD development. There are three clinical courses after ISD withdrawal: regressive LPD without relapse/regrowth (R-G), regressive LPD with RRE (R/R-G), and persistent LPD (P-G). The majority of EBV+ diffuse large B-cell lymphomas are classified in R-G, whereas classic Hodgkin lymphoma is generally classified in R/R-G. Polymorphic LPD (P-LPD) in MTX-LPD develops with heterogeneous pathological features similar to monomorphic LPD. Chemotherapy for MTX-LPD is selected according to that for *de novo* LPD, although the strategy for aggressive P-LPD and non-specific LPD is not well established. The absolute lymphocyte count in the peripheral blood has been suggested as a candidate marker for MTX-LPD development and RRE. Several clinical issues, including correct diagnosis among overlapping clinicopathological features in MTX-LPD and clinical management of LPD by ISDs other than MTX, require further investigation.

Keywords: clinical management, iatrogenic immunodeficiency-associated lymphoproliferative disorders, methotrexate, rheumatoid arthritis

OTHER IATROGENIC IMMUNODEFICIENCY-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS (OIIA-LPD)

Immune deficiency is an important factor in the pathogenesis of LPD among a number of influencing events. According to the World Health Organization (WHO) classification, immunodeficiency-associated LPD (IA-LPD) is classified into four subtypes; LPD associated with primary immune disorders, lymphomas associated with HIV infection, post-transplant LPD (PTLD), and OIIA-LPD.[1,2] OIIA-LPD is defined as lymphoid proliferations or lymphomas that develop in patients receiving immunosuppressive drugs (ISDs) for autoimmune diseases (AIDs) or conditions other than the post-transplant setting in the 2008 WHO classification.[1] However, the ISD-mediated LPD category remains controversial because of the difficulty in confirming a direct effect of ISDs based on the high risk of LPD development in patients with AIDs as a natural clinical course. The standardized incidence ratio (SIR) of rheumatoid arthritis (RA) is 2-20-fold that in the control healthy population.[3-12] In particular, the incidence rate is high in Japan. For example, the SIR in the NinJa study,[6] SUCURE study,[8] and IORRA cohort[10] in Japan was 3.43, 6.18, and 4.61, respectively. In addition, the disease severity and accumulated inflammatory activity of RA may be related to LPD development.[13] Although different AIDs are treated using different ISDs in OIIA-LPD, there is no direct evidence of the pathogenesis of LPD, except for LPD regression after ISD withdrawal. Methotrexate (MTX) is recognized as the ISD associated with LPD in the WHO classification (2001),[14] categorized as the MTX-LPD disease entity. The category of OIIA-LPD was defined in the 2008 and 2017 WHO classifications[1,2] to replace the concept of MTX-LPD. Among ISDs, MTX and anti-tumor necrosis factor inhibitors (TNFi) are candidates initiating LPD.[1,2]

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OIIA-LPD originates from many cell types, including B, T, and natural killer (NK) cells.[1,2,14] The major types of monomorphic LPD (M-LPD) are diffuse large B cell lymphoma (DLBCL) and classic Hodgkin lymphoma (CHL), comprising 58% and 15.3% of 274 cases of OIIA-LPD, respectively, in the 2017 WHO classification.[1] Rare subtypes of LPD include polymorphic features, such as polymorphic/lymphoplasmacytic infiltrates (P/L-I), Hodgkin-like lesions (HLL), and Epstein-Barr virus-positive mucocutaneous ulcer (EBVMCU), which comprise 9.9%, 2.2%, and 3.3%, respectively.[1] Although non-destructive LPD (ND-LPD), defined as PTLD in the WHO classification,[1,2] is not described in OIIA-LPD, it accounts for 10-15% of MTX-LPD according to previous reports.[15,16] Although ISDs other than MTX promote LPD development based on previous reports, assessment of such non-MTX-LPD is difficult because of the small number of cases. Thus, this article focuses on the management of MTX-LPD in OIIA-LPD. In addition, although the WHO classification does not separate DLBCL subtypes, such as EBV+DLBCL and DLBCL-NOS, in OIIA-LPD,[1,2] we analyzed them specifically focusing on the differences between *de novo* DLBCL and MTX-DLBCL.

LPD REGRESSION AFTER ISD WITHDRAWAL

LPD regression after ISD withdrawal is one of the unique characteristics, suggesting a direct influence on the pathogenesis of LPD development. Although this phenomenon is also described in other disorders like PTLD,[17] it mainly develops in patients with MTX-LPD. LPD regression after MTX withdrawal is observed in 20-70% of patients. In the 2017 WHO classification, 40.4% of 188 patients with OIIA-LPD demonstrated LPD regression.[1] Among 545 patients with MTX-LPD collected in a study by Pfizer, Japan, LPD regression after MTX withdrawal comprised 86.2% of the 302 evaluable events.[18] As more than 50% of the patients without relapse/regrowth events (RRE) after LPD regression do not require additional chemotherapy and have a superior overall survival (OS),[16,19] watchful wait therapy (WW) is recommended initially when MTX-LPD develops. To clarify the clinical management of MTX-LPD, which includes avoiding additional therapy for regressive LPD, we propose three clinical courses after ISD withdrawal: LPD regression after ISD withdrawal without RRE (regressive group, R-G), LPD regression after ISD withdrawal with RRE (relapse/regrowth group, R/R-G), and persistent LPD after ISD withdrawal (persistent group, P-G) (Figure 1).[16,19] In these reports, the ratio of the three groups was similar. In R-G and R/R-G, but not P-G, the direct influence of ISDs on the pathogenesis of LPD development was suggested because they exhibited LPD regression phenomenon. In P-G, *de novo* LDP and irreversible MTX-LPD due to ISDs are involved, although it is difficult to discriminate between them. Regarding this point, the differences between *de novo* LPD and MTX-LPD have been investigated in several studies.[20-23] Carreras *et al*. demonstrated differences in the phenotype and genetic characteristics of MTX-LPD-DLBCL and *de novo* DLBCL such as a genomic profile with 3q and 12 gains, 13q loss, different expression levels of relevant pathogenic biomarkers, and a microenvironment with high numbers of cytotoxic T lymphocytes and M2 macrophages.[21] In other studies, most MTX-DLBCL cases had an activated-B-cell immunophenotype, especially Epstein-Barr virus (EBV) - positive cases, and MTX-EBV+DLBCL commonly expressed CD30.[22,23] Ejima-Yamada *et al*. found that EBV infection in MTX-B cell-LPD in patients with RA is associated with a lower incidence of CpG island methylator phenotype and B-cell lymphoma 2 expression, resulting in LPD regression after MTX withdrawal and improved prognoses.[24]

The three clinical groups have different trends in clinical parameters: serum C-reactive protein (CRP) and serum soluble interleukin-2 receptor (sIL-2R) are increased in R/R-G, whereas serum lactate dehydrogenase (LDH), CRP, and sIL-2R are increased in P-G.[16,19] Furthermore, the OS for R-G is significantly better than that for the other two groups.[16] Thus, RRE is an important event among patients with regressive LPD after ISD withdrawal. According to previous reports, RRE develops within 2-3 years after LPD regression.[15,16,19,25] In our study, the rate of regressive LPD (R-G and R/R-G) was different for each LPD of MTX-LPD; a higher rate was observed for MTX-EBV+DLBCL, MTX-P-LPD, MTX-EBVMCU and MTX-ND-LPD, whereas MTX-DLBCL-NOS had a lower rate.

Recent studies have suggested that lymphocytes play an important role in the pathogenesis of LPD regression after ISD.[26-30] Inui *et al*. reported recovery of lymphocytes in peripheral blood (PB) in patients with regressive LPD after MTX, although not in patients with P-G.[26] Saito *et al*.

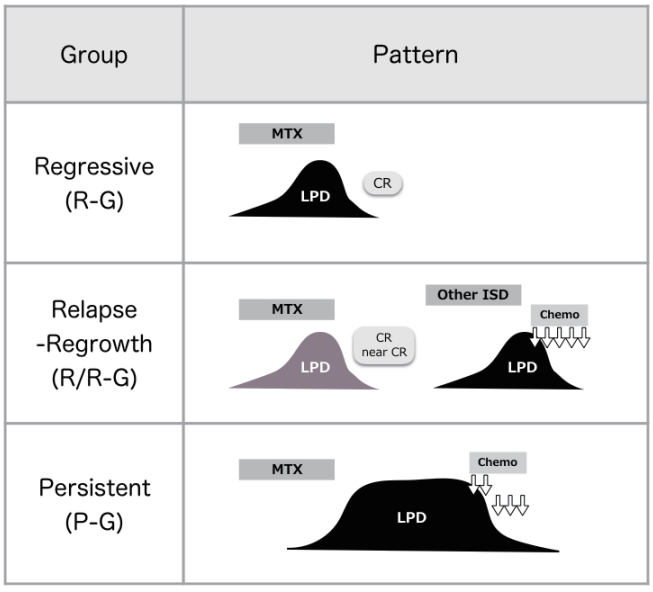

Fig. 1. Three clinical courses of methotrexate-associated lymphoproliferative disorders (MTX-LPD)[19]
Three clinical courses are observed in patients with MTX-LPD after immunosuppressive drug (ISD) withdrawal: regressive LPD without relapse/regrowth event (RRE, regressive group, R-G), regressive LPD with RRE (R/R-G), and persistent LPD (P-G). CR, complete response; Chemo, chemotherapy.

confirmed this finding among patients with MTX-LPD, and reported that the recovered lymphocytes were composed of CD8+ T cells and natural killer (NK) cells.[27] They also demonstrated a decrease in the absolute lymphocyte count (ALC) in PB towards the time of LPD development in patients with regressive LPD, suggesting a key role of lymphocytes in the pathogenesis of MTX-LPD.[27] Furthermore, the change in lymphocytes may influence RRE. Among 43 patients with MTX-LPD, the ALC gradually decreased toward RRE in R/R-G, but not in R-G.[30] Regarding prognosis factors, an ALC of < 600/μL in PB is one of the prognostic factors for *de novo* CHL.[31] The value of ALC as a prognostic factor has also been confirmed for several lymphomas.[32-35] Taken together, lymphocytes in PB are suggested to be one of the triggers in the development of MTX-LPD.

CLINICAL MANAGEMENT OF MTX-LPD

The clinical management of MTX-LPD is illustrated in Figure 2, according to the previous reports in clinical practice. After WW following cessation of ISDs, patients without RRE do not require additional therapy (R-G, [1]), whereas additional chemotherapy is administered at the time of RRE (R/R-G, [2]). Chemotherapy is also considered for patients with non-regressive LPD under WW (P-G, [3]). On the other hand, the evaluation of WW has been considered for OIIA-LPD since around 2010, and it is not suitable for patients with aggressive LPD with severe organ damage. Thus, chemotherapy is initiated without confirmation of the regressive phase under these conditions (chemotherapy group, Ch-G, [4]). Furthermore, chemotherapy is initiated if the LPD has an inadequate response under LPD regression (included in P-G, [5]). Based on reports of M-LPD in MTX-LPD, including DLBCL and CHL, chemotherapy is selected according to the strategy of *de novo* LPD. In contrast, little information is available about patients with aggressive polymorphic LPD (P-LPD), such as P/L-I, HLL, and EBVMCU, in MTX-LPD. Based on previous reports, chemotherapy for P-LPD is selected according to the similar pathological features to DLBCL or CHL, as described in later reports of MTX-P-LPD and MTX- EBVMCU. Although the clinical outcome of patients with ND-LPD is as good as that of patients with P-LPD, aggressive ND-LPD is observed.[15,16] Similar to P-LPD, chemotherapy for such aggressive cases is based on the diagnosis of similar pathological features in M-LPD (described in the MTX-ND-LPD section). However, the relevance of this concept of aggressive LPD in P-LPD and ND-LPD has yet to be evaluated.

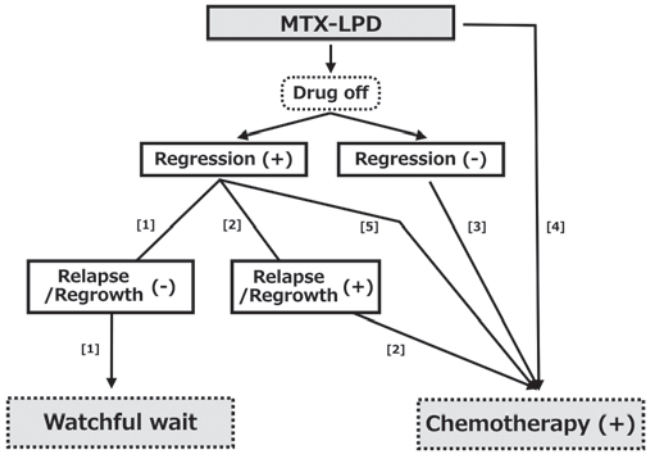

Fig. 2. Clinical management of methotrexate-associated lymphoproliferative disorders (MTX-LPD)
The first step after MTX-LPD development is watchful waiting (WW) following the cessation of immunosuppressive drugs (ISDs). Additional therapy is not required for patients without relapse/regrowth event (RRE, R-G, [1]), but chemotherapy is administered when RRE develops (R/R-G, [2]). Chemotherapy is also considered for patients with non-regressive LPD under WW (persistent group, P-G, [3]). On the other hand, WW therapy is not suitable for patients with aggressive LPD, and chemotherapy is initiated without confirmation of the regressive phase (chemotherapy group, Ch-G, [4]). Furthermore, chemotherapy is initiated if the LPD remains in partial response or exhibits a low response during regression (included in P-G, [5]). The details are also described in the text.

Regarding the administration of ISDs at the time of LPD development, all ISDs are basically withdrawn because identifying the drug responsible for LPD is difficult. The majority of OIIA-LPD is MTX-LPD in RA. Although LPD associated with ISDs, except MTX (non-MTX-LPD), may develop, our understanding of non-MTX-LPD is limited because of the small number of patients with combinations of AIDs and ISDs. In addition, the history of MTX administration is carefully assessed among non-MTX-LPD patients because RRE occurs within several years after the withdrawal of MTX. In this article, the clinical features of MTX-LPD are listed based on data summarized from previous reports that described the clinical information such as the clinical patterns of R-G, R/R-G, P-G, and Ch-G.

MTX-DLBCL

The common LPD in OIIA-LPD is DLBCL (30-60%). According to the WHO classification, DLBCL comprises several subtypes, including not-otherwise-specified (NOS) and EBV positive (EBV+) subtypes.[1] In this article, we analyzed the clinical features of MTX-DLBCL, including subtypes such as MTX-EBV+ DLBCL and MTX-DLBCL-NOS, and highlighted the clinical aspects in Tables 1 and 2.[16,25,36-55] Although the WHO classification described DLBCL as DLBCL-type including DLBCL and LPDs similar to the pathological features of DLBCL in OIIA,[25] in our study demonstrated DLBCLs as MTX-EBV+ DLBCL and MTX-DLBCL-NOS. The number of patients with MTX-EBV+DLBCL and MTX-DLBCL-NOS were 66 and 50, respectively (Tables 2, 3). Thus, the rate of EBV positivity was 57% among patients with MTX-DLBCL, although this value varies in previous studies. For example, EBV positivity in 24.1% of 29 patients,[56] 45% of 42 patients,[57] and 82% of 34 patients[25] was reported. The incidence of *de novo* EBV+ DLBCL among all the DLBCL cases was <5-15% of Asian and Latin American patients and <5% of Western patients.[1,2] Thus, the rate of EBV positivity is higher in MTX-DLBCL. Although MTX-EBV+DLBCL is female dominant (71%), MTX-DLBCL-NOS has a lower incidence

Table 1. Clinical features of diffuse large B cell lymphoma (DLBCL) in methotrexate associated lymphoproliferative disorders (MTX-LPDs)

Subtype	Author	Year	N	Sex			Age		Basal disease				MTX duration (y)		Clinical State					Ref
									Types		Duration (y)									
				M	F	ND	Mean	Range	RA	Other	Mean	Range	Mean	Range	I	II	III	IV	E	
MTX-EBV+ DLBCL	Kojima	2006	1	1	0	0	64	-	1	-	14	-	7	-	1	0	0	0	0	36
	Miyazaki	2007	3	0	3	0	69	68-71	3	-	12.9	7.3-19.3	6.1	2.8-8.3	1	2	0	0	0	37
	Jois	2007	1	0	1	0	48		0	CD	1.3	-	1.3	-	0	0	0	1	0	38
	Ogasawara	2007	1	1	0	0	71	-	1	-	20	-	ND	-	0	0	0	1	0	39
	Rizzi	2009	4	0	4	0	63	46-86	4	-	18.5	11-24	1.5	0.9-3	0	0	2	2	0	40
	Ishida	2013	1	0	1	0	76	-	1	-	10	-	10	-	0	0	0	1	0	41
	Yamakawa	2014	2	0	2	0	64	61-67	2	-		NR	8.7	1.3-16	1	0	1	0	0	42
	Kameda	2014	2	1	1	0	66	61-71	2	-	15.5	14-17	10.5	9-12	2	0	0	0	0	43
	Kawano	2014	1	0	1	0	74	-	1	-	10	-	4.1	-	0	0	0	1	0	44
	Kudoh	2014	1	0	1	0	75	-	1	-	5	-	5	-	0	0	0	1	0	45
	Shimizu	2015	2	1	1	0	69	63, 75	1	DM+SjS	9	ND, 9	6.5	4, 9	0	0	0	0	2	46
	Ikeda	2016	1	0	1	0	78	-	1	-	18	-	2	-	1	0	0	0	0	47
	Matsumoto	2016	1	1	0	0	63	-	1	-	10	-	10	-	0	0	0	1	0	48
	Hatano	2017	1	1	0	0	61	-	1	-	7	-	6	-	0	0	0	1	0	49
	Takei	2017	1	0	1	0	65	-	1	-	ND	-	7	-	0	0	0	1	0	50
	Gion	2017	27	8	19	0	69.2	55-82	27	-		NR		NR	4	4	2	17	0	25
	Oebisu	2018	1	0	1	0	46	-	1	-	5	-	5	-	0	0	0	1	0	51
	Suzuki	2018	1	0	1	0	66	-	1	-	7	-	7	-	0	0	0	1	0	52
	Tokuhira	2018	14	5	9	0	70.7	54-88	13	PV1	15.3	1.3-32.4	6.7	1.1-15.1	2	1	1	10	0	16
	Total		66	19	47	0	68		64	3	13.5		6.1		12	7	6	39	2	
MTX-DLBCL-NOS	Ebeo	2003	1	1	0	0	54	-	1	-	12	-	5	-	0	0	0	1	0	53
	Kojima	2006	3	0	3	0	66	65-68	3	-	13.7	1-35	2	1-3	0	0	0	3	0	36
	Miyazaki	2007	6	3	3	0	65	53-77	6	-	3.2	1.6-13.4	4.3	0.8-9.5	0	1	3	2	0	37
	Rizzi	2009	4	2	1	1	63	58-69	2	PV2	12	5-20	5.5	3-7	2	0	0	0	2	40
	Yamakawa	2014	7	3	4	0	68	52-74	7	-		ND	4.1	0.6-8.2	1	4	0	2	0	42
	Kameda	2014	4	2	2	0	70	61-80	4	-	17.5	10-34	10.8	7-16	2	0	1	1	0	43
	Kawano	2014	4	3	1	0	65.5	60-76	4	-	8.8	3-15	4.8	3-7	1	0	1	2	0	44
	Kawahara	2015	1	1	0	0	64	-	1	-	2	-	2	-	0	0	0	1	0	54
	Miyagawa	2015	1	0	1	0	56	-	1	-	7	-	2	-	0	0	0	1	0	55
	Gion	2017	6	2	4	0	66	58-72	6	-		NR		NR	0	1	0	5	0	25
	Tokuhira	2018	13	3	10	0	67	41-77	12	SLE1	8.4	3.3-19.1	4.2	1.1-8.4	0	2	1	10	0	16
	Total		50	20	29	1	66		46	3	11.1		5.4		6	8	6	28	2	

M, men; F, female, EBV, Epstein-Barr virus; NOS, not otherwise specified; NR, not recorded; RA, rheumatoid arthritis; CD, Crohn disease; DM, dermatomyositis; SjS, Sjögren syndrome; PV, psoriasis vulgaris; SLE, systemic lupus erythematosus; Ref, reference.

Table 2. Clinical outcome of diffuse large B cell lymphoma (DLBCL) in methotrexate (MTX) associated lymphoproliferative disorders.

Subtype	Author	Year	N	Pattern					Chemotherapy	Alive/Dead			Alive								Dead								
													Pattern				Duration (M)				Pattern					Duration (M)			
				R	R/R	P	Ch	Other		A	D	NR	R	R/R	P	Ch	R	RR	P	Chemo	R	R/R	P	Ch	Other	R	RR	P	Chemo
MTX-EBV+ DLBCL	Kojima	2006	1	0	0	0	1*	0	* NR	1	0	0	0	0	0	1	-	-	-	4	0	0	0	0	-	-	-	-	-
	Miyazaki	2007	3	2	0	1*	0	0	* R-CHOP	3	0	0	2	0	1	0	109, 18	-	26	-	0	0	0	0	-	-	-	-	-
	Jois	2007	1	1	0	0	0	0		1	0	0	1	0	0	0	8	-	-	-	0	0	0	0	-	-	-	-	-
	Ogasawara	2007	1	0	0	0	1*	0	* CHOP	1	0	0	0	0	0	1	-	-	-	24	0	0	0	0	-	-	-	-	-
	Rizzi	2009	4	4	0	0	0	0		4	0	0	4	0	0	0	16, 48, 11, 30	-	-	-	0	0	0	0	-	-	-	-	-
	Ishida	2013	1	0	0	0	1*	0	* R-THP-COP	1	0	0	0	0	0	1	-	-	-	30	0	0	0	0	-	-	-	-	-
	Yamakawa	2014	2	0	0	0	2*	0	* R-CHOP	1	1	0	0	0	0	1	-	-	-	45	0	0	0	1	-	-	-	-	90
	Kameda	2014	2	1	0	0	1*	0	* R-CHOP	2	0	0	1	0	0	1	15	-	-	6	0	0	0	0	-	-	-	-	-
	Kawano	2014	1	0	0	1*	0	0	* Radiation	1	0	0	0	0	1	0	-	-	ND	-	0	0	0	0	-	-	-	-	-
	Kudoh	2014	1	0	0	0	1*	0	* R-CHOP	1	0	0	0	0	0	1	-	-	-	48	0	0	0	0	-	-	-	-	-
	Shimizu	2015	2	2	0	0	0	0		1	1	0	1	0	0	0	96	-	-	-	1	0	0	0	-	2	-	-	-
	Ikeda	2016	1	0	0	1*	0	0	* R-CHOP	1	0	0	0	0	1	0	12	-	-	-	0	0	0	0	-	-	-	-	-
	Matsumoto	2016	1	1	0	0	0	0		1	0	0	1	0	0	0	7	-	-	-	0	0	0	0	-	-	-	-	-
	Hatano	2017	1	1	0	0	0	0		1	0	0	1	0	0	0	24	-	-	-	0	0	0	0	-	-	-	-	-
	Takei	2017	1	1	0	0	0	0		1	0	0	1	0	0	0	12	-	-	-	0	0	0	0	-	-	-	-	-
	Gion	2017	27	20	0	2*	4**	1***	* R-CHOP, ** R-THP-CO 1, R-CHOP 3, *** found on autopsy	27	0	0	20	1	2	4	Mean 30.8 (2.9-78)	5.2	6, 30	3.3, 10, 4, 3.6	0	0	0	0	-	-	-	-	-
	Oebisu	2018	1	0	1*	0	0	0	* R-CHOP+AlloSCT	1	0	0	0	1	0	0	-	ND	-	-	0	0	0	0	-	-	-	-	-
	Suzuki	2018	1	0	0	1*	0	0	* Steroid pulse	1	0	0	0	0	1	0	1.5	-	-	-	0	0	0	0	-	-	-	-	-
	Tokuhira	2018	14	8	1*	5**	0	0	* R-CHOP, ** CHOP3, PSL 2	10	4	0	7	1	2	0	Mean 70 (22-145)	24	17, 208	-	1	0	3	0	-	70	-	1, 1, 11	-
	Total		66	41	2	11	11	1		60	6	0	39	3	8	10					2	0	3	1	0				
MTX-DLBCL-NOS	Ebeo	2003	1	1	0	0	0	0		1	0	0	1	0	0	0	24				0	0	0	0	-	-	-	-	-
	Kojima	2006	3	0	0	0	3*	0	* NR	1	2	0	0	0	0	1	-	-	-	48	0	0	0	2	-	-	-	-	12, 4
	Miyazaki	2007	6	0	0	6*	0	0	* R-CHOP 5, CyclOBEAP 1	6	0	0	0	0	6	0	-	-	9, 58, 43, 37, 3, 5	-	0	0	0	0	-	-	-	-	-
	Rizzi	2009	4	1	0	0	1*	2**	* CHOP **NR	2	0	2	1	0	0	1	6	-	-	15	0	0	0	0	-	-	-	-	-
	Yamakawa	2014	7	2	0	0	5*	0	* Rituximab 1, R-CHOP 5	6	1	0	2	0	0	4	32, 14	-	-	48, 84, 8, 15	0	0	0	1	-	-	-	-	27
	Kameda	2014	4	1	0	0	3*	0	* R-CHOP 3	2	2	0	1	0	0	1	15	-	-	30	0	0	0	2	-	-	-	-	ND, 15
	Kawano	2014	4	1	1*	2**	0	0	* R-CHOP, ** Rituximab, R-CHOP	4	0	0	1	1	2	0	35	31	10, 23	-	0	0	0	0	-	-	-	-	-
	Kawahara	2015	1	1	0	0	0	0		1	0	0	0	0	1	0	24	-	-	-	0	0	0	0	-	-	-	-	-
	Miyagawa	2015	1	0	0	1*	0	0	* R-CHOP	1	0	0	1	0	0	0	-	-	6	-	0	0	0	0	-	-	-	-	-
	Gion	2017	6	2	0	2*	1**	1***	* R-CHOP, CHOP, ** R-CHOP, *** found on autopsy	3	3	0	2	0	1	0	1.8, 29	-	10	-	0	0	1	1	1	-	-	22	78
	Tokuhira	2018	13	4	2*	7**	0	0	* CHOP 2, ** PSL 2, R-CHOP 5	8	5	0	4	1	3	0	25, 30, 33, 68	41	21, 21, 24	-	0	1	4	0	-	-	18	1, 2, 3, 55	-
	Total		50	13	3	18	13	3		35	13	2	13	2	13	7					0	1	5	6	1				

EBV, Epstein-Barr virus; N NOS, not otherwise specified; NR, not recorded; R, regressive group; R/R, relapse/regrowth group; P. persistent group; Ch, chemotherapy-G; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-THP-COP, rituximab, cyclophosphamide, pirarubicin, vincristine and prednisolone; alloSCT, allogenic stem cell transplantation; CyclOBEAP, cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin, and prednisolone; A, alive; D, dead.

Table 3. Clinical features of classical Hodgkin lymphoma (CHL), polymorphic lymphoproliferative disorders (P-LPD), and non-specific LPD (NS-LPD)

Subtype	Author	Year	N	Sex		Age		Basal disease				MTX duration		Clinical State				EBV						Comment	Ref
								Types		Duration								Ratio		Latency					
				M	F	Mean	Range	RA	Other	Mean	Range	Mean	Range	I	II	III	IV	+	-	I	II	III			
MTX-CHL	Kojima	2006	3	1	2	37	52-63	3		14.7	9-28	8.3	7-9	1	0	2	0	2	1		NR				36
	Rizzi	2009	7	1	6	45	6-70	5	JRA 2	10	1-24	2.9	0.7-10	1	2	2	2	5	1		NR				40
	Loo	2013	6	1	5	53	25-77	5	PM 1		NR		NR	1	1	1	3	4	2		NR				72
	Yamakawa	2014	3	1	2	69	65-76	3			NR	3.9	2.3-5.5	0	2	1	0	1	2	0	2	0			42
	Kameda	2014	2	1	1	72	65-79	2		10	8-12	11.5	15-18	0	0	0	2	1	1		NR				43
	Takasumi	2015	1	0	1	68	-	1	-	14	-	7	-	0	0	0	1	1	0	0	1	0			73
	Tsukazaki	2017	1	0	1	88	-	1	-	14	-	6	-	0	0	0	1	1	0		NR				74
	Gion	2017	17	4	13	65	84	17	-		NR		NR	4	0	8	5	14	3		NR				25
	Eso	2018	1	1	0	83	-	1	-	6	-	6	-	0	0	0	1	1	0		NR				75
	Tokuhira	2018	10	3	7	65	53-79	10	-	15.5	5.6-39	5.8	2.8-5.6	0	1	1	8	8	2		NR				16
	Total		51	13	38	62		48	3	13		5.6		7	6	15	23	38	12	0	3	0			
MTX-polymorphic LPD	Kojima	2006	3	1	2	63	57-73	3	-		NR	3.3	2-5	3	0	0	0	3	0		NR		P-LPD		36
	Komatsuda	2008	1	0	1	63	-	1	-	14	-	14	-	0	0	0	1	1	0		NR		HLL		81
	Rizzi	2009	2	1	1	40	33-47	2	-	8	2.9-13	5	4.9-5	0	0	0	1	2	0		NR		HLL		40
	Tokuhira	2012	1	1	0	69	-	1	-		-	1.1	-	0	0	1	0	1	0				HLL		19
	Yamakawa	2014	2	1	1	75	71-79	2	-		NR	8	8-8	1	0	1	0	2	0	1	0	1	P-LPD		42
	Kawano	2014	1	0	1	56	-	1	-	5	-	2.5	-	0	0	0	1			ND			HLL		44
	Ohkura	2015	1	1	0	70	-	1	-	20	-	8	-	1	0	0	0	1	0		NR		HLL		82
	Yamakawa	2016	1	1	0	78	-	1	-	12	-	4	-	0	0	0	1	1	0		NR		P-LPD		83
	Tsukui	2018	5	0	5	72	63-78	5	-		NR	10	2-15		ND		3	4	0		NR		P-LPD		84
	Total		17	6	11	65		17	0	11		7.2		5	0	2	7	15	0	1	0	1			
MTX-NS-LPD	Tokuhira	2018	9	4	5	65	45-80	8	PV 1	16	5.4-37.8	8.9	4.2-16.3	3	3	0	3	4	3		NR				16

EBV, Epstein-Barr virus; NR, not recorded; RA, rheumatoid arthritis; JRA, juvenile rheumatoid arthritis; PM, polymyositis; PV, psoriasis vulgaris: Ref, reference.

rate in females (59%). Mean ages at the development of MTX-DLBCL are similar between MTX-EBV+DLBCL and MTX-DLBCL-NOS (66 and 68 years, respectively, Table 1), which is similar to *de novo* DLBCL.[58] In both types of MTX-DLBCL, the most common AID was RA, and the duration of AID and MTX administration was over 10 and 5 years, respectively. Two-thirds of the patients had clinical stage (CS) 3 or 4 MTX-DLBCL (Table 1). Regarding the laboratory data for MTX-DLBCL in our previous study,[16] the median serum levels of LDH, CRP, and sIL-2R in EBV+DLBCL and DLBCL-NOS were 240 IU/L, 1.4 mg/dL, 1440 U/mL, and 208 IU/L, 4.7 mg/dL, and 1525 U/mL, respectively, demonstrating similar trends between the two types of MTX-DLBCL. The EBV latency in MTX-EBV+DLBCL was type II dominant.[58]

The clinical outcomes of MTX-DLBCL are listed in Table 2. The ratios of R-G, R/R-G, P-G, and Ch-G in MTX-EBV+DLBCL and MTX-DLBCL-NOS were 62%, 3%, 17%, 17%, and 26%, 6%, 36%, 26%, respectively. The rate of regressive LPD (R-G+R/R-G) was higher in MTX-EBV+DLBCL than in MTX-DLBCL-NOS (65% and 32%, respectively), supporting the previous report.[58] The ratio of patients with RRE in MTX-EBV+DLBCL and MTX-DLBCL-NOS was low (4% and 6%, respectively). The survival rate was higher for MTX-EBV+DLBCL than for MTX-DLBCL-NOS (91% and 60%, respectively) (Table 2). In addition, poorer survival rates were noted for P-G and Ch-G of MTX-DLBCL-NOS (72% and 53%, respectively), whereas higher survival rates were found for R-G of MTX-EBV+DLBCL and MTX-DLBCL-NOS (95% and 100%, respectively). As *de novo* EBV+DLBCL in elderly patients has a poor prognosis,[59-61] the clinical outcome of MTX-EBV+DLBCL reflects a superior OS. Regarding the pathological heterogeneity of OIIA-LPD, LPD resembling DLBCL includes P-LPD, such as EBVMCU, P/L-I, and HLL.[1] Furthermore, the definition of EBVMCU includes the clinical manifestations, such as ulceration with EBV-positive cells, whereas P-LPD has similar pathological features to EBVMCU without the clinical manifestation of skin or mucosal ulceration. In addition, the OS for P-LPD was as good as that for EBVMCU. Thus, discriminative clinicopathological diagnosis of EBV+LPD, including EBV+DLBCL, P-LPD, and EBVMCU, in OIIA-LPD remains vague. Previous reports found a similar OS between MTX-EBV+DLBCL and MTX-DLBCL-NOS.[16,57] In our series, several patients with MTX-EBV+DLBCL or MTX-DLBCL-NOS in P-G died due to progressive disease.[16] Due to the delay of diagnosis of MTX-DLBCL when the disease entity of MTX-LPD was not well recognized, insufficient chemotherapy, such as prednisolone monotherapy, was consequently given to the patients, resulting in poor outcomes. Therefore, withdrawal of ISDs should be first performed to prevent LPD aggravation when manifestations resembling MTX-LPD, such as fever, lymphoadenopathy, or respiratory symptoms, and laboratory abnormalities, such as increased serum LDH, CRP, and sIL-2R, develop (described in "Clinical-MTX-LPD"). The standard therapy for MTX-DLBCL patients with P-G or Ch-G is R-CHOP-based chemotherapy (Table 2). Rituximab monotherapy is occasionally given to MTX-DLBCL patients considering the LPD and AID activity in clinical practice.[44,62] Although rituximab monotherapy can be effective against AIDs, especially RA, it is not suitable to cure DLBCL. Other MTX-DLBCL cases are also reported.[24,56-59,63-71]

MTX-CHL

Fifty-one cases of MTX-CHL from 11 reports are summarized in Tables 3 and 4.[16,25,36,40,42,43,72-75] Although one study described the pathological diagnosis as CHL-type,[25] such cases were categorized into MTX-CHL in this article. Thirty-eight of the patients were female, and the mean age was 62 years, which is older than that for *de novo* CHL.[58] Ninety-four percent of patients (48/51) had RA or other AIDs, such as juvenile RA (JRA, N=1), and polymyositis (PM, N=1). The mean duration of AID and MTX administration was 13 years and 5.6 years, respectively. The rate of CS 3 and 4 was 75% (41/55). EBV positivity was noted in 76% (38/51). Among patients with MTX-CHL in our series, the median serum LDH, CRP, and sIL-2R levels were 214 IU/L, 12.3 mg/dL, and 3110 U/mL, respectively.[16] The CRP level was significantly higher in CHL than in DLBCL.[16] Clinical outcomes of MTX-CHL are shown in Table 4. The incidence rates of R-G, R/R-G, P-G, and Ch-G were 14%, 40%, 24%, and 21%, respectively. A lower incidence rate of R-G (14%) and a higher rate of R/R-G (40%) were noted for MTX-CHL than for DLBCL, suggesting frequent RRE in MTX-CHL. Chemotherapy was administered to 86% of patients with MTX-CHL (Table 4). Kuita *et al*. compared 26 patients with MTX-CHL among 219 patients with MTX-LPD, and all of them received chemotherapy with a median progression-free survival of 5 months.[15] Chemotherapy was based on ABVD, although R-CHOP was also given (Table 4). Regarding OS, 78% of MTX-CHL patients (39/50) survived, although the survival rate differs among studies. For example, MTX-CHL patients in our series with a relatively long observation period (median, 4.4 years) had a poorer OS (5-year OS, 33%)[16] than those in other studies.[15,25] The survival rate in R-G, R/R-G, P-G, and Ch-G was 100%, 65%, 67%, and 100%, respectively (Table 4). As the observation duration of 4 MTX-CHL patients in R-G was shorter than 2 years, the ratio in R-G may further decrease during the long-follow up. The pathological features of P-LPD, including HLL and EBVMCU, often resemble those of CHL, with Reed-Sternberg-like cells, explaining the difficulty in diagnosis of MTX-CHL. In contrast, the lower rate of R-G in MTX-CHL may be because P-LPD cases are not categorized as MTX-CHL.

Regarding the clinical management, the OS is poorer for MTX-CHL patients in R/R-G (65%) than those in Ch-G (100%) (Table 4). If RRE occurs at a higher rate in MTX-CHL, as found in this analysis, chemotherapy without WW or during WW is one of the options to improve OS, but such a strategy may be less advantageous for patients in R-G (14%). Several studies have investigated predictive surrogate

Table 4. Clinical outcome of classical Hodgkin lymphoma (CHL), polymorphic lymphoproliferative disorders (P-LPD), and non-specific LPD (NS-LPD).

Subtype	Author	Year	N	Pattern					Therapy	Alive/Dead			Alive								Dead							
													Pattern				Duration (M)				Pattern				Duration (M)			
				R	R/R	P	Ch	ND		A	D	ND	R	R/R	P	Ch	R	RR	P	Chemo	R	R/R	P	Ch	R	RR	P	Chemo
MTX-CHL	Kojima	2006	3	0	0	0	3*	0	* NR	3	0	0	0	0	0	3	-	-	-	66, 74, 24	0	0	0	0	-	-	-	-
	Rizzi	2009	6	2	1*	2*	1*	0	*NR	6	0	0	2	1	2	1	12, 12	12	NR	18	0	0	0	0	-	-	-	-
	Loo	2013	6	0	0	0	5*	1	* ABVD 3, CHOP 1, COPP 1	5	0	1	0	0	0	5	-	-	-	72, 12, 27, 72, 72	0	0	0	0	-	-	-	-
	Yamakawa	2014	3	1	2	0	0	0		2	1	0	1	1	0	0	1	79	-	-	0	1	0	0	-	17	-	-
	Kameda	2014	2	0	1*	0	1*	0	*ABVD	2	0	0	0	1	0	1	-	15	-	90	0	0	0	0	-	-	-	-
	Takasumi	2015	1	0	0	1*	0	0	* No therapy due to PD	0	1	0	0	0	0	0	-	-	-	-	0	0	1	0	-	1	-	-
	Tsukazaki	2017	1	0	0	0	1*	0	* ABVD	1	0	0	0	0	0	1	24	-	-	-	0	0	0	0	-	-	-	-
	Gion	2017	17	4	7*	6**	0	0	* ABVD, ** ABVD, 6, R-CHOP base 1	16	1	0	4	7	5	0	-	-	-	-	0	0	1	0	-	-	-	-
	Eso	2018	1	0	0	1*	0	0	*rituximab→brentuximab vedotin→nivolumab	0	1	0	0	0	0	0	-	-	-	-	0	0	1	0	-	-	ND	-
	Nakazato	2018	1	0	0	1*	0	0	* ABVD→brentuximab vedotin	1	0	0	0	0	1	0	-	-	12	-	0	0	0	0	-	-	-	-
	Tokuhira	2018	10	0	9*	1*	0	0	* ABVD	3	7	0	0	3	0	0	-	61, 67, 177	-	-	0	6	1	0	-	Mean 28 (10-58)	24	-
	Total		51	7	20	12	11	1		39	11	1	7	13	8	11					0	7	4	0				
MTX-polymorphic LPD	Kojima	2006	3	2	1*	0	0	0	* NR	2	1	0	2	0	0	0	3, 1	-	-	-	0	1	0	0	-	12	-	-
	Komatsuda	2008	1	1	0	0	0	0		1	0	0	1	0	0	0	5	-	-	-	0	0	0	0	-	-	-	-
	Rizzi	2009	2	2	0	0	0	0		2	0	0	2	0	0	0	9, ND	-	-	-	0	0	0	0	-	-	-	-
	Tokuhira	2012	1	0	1*	0	0	0	* ABVD, C-MOPP, CHOP	0	1	0	0	0	0	0	-	-	-	-	0	1	0	0	-	7	-	-
	Yamakawa	2014	2	1	0	0	1*	0	* R-CHOP	2	0	0	1	0	0	1	37	-	-	9	0	0	0	0	-	-	-	-
	Kawano	2014	1	0	1*	0	0	0	* ABVD	1	0	0	0	1	0	0	-	21	-	-	0	0	0	0	-	-	-	-
	Ohkura	2015	1	1	0	0	0	0		1	0	0	1	0	0	0	12	-	-	-	0	0	0	0	-	-	-	-
	Yamakawa	2016	1	1	0	0	0	0		1	0	0	1	0	0	0	4	-	-	-	0	0	0	0	-	-	-	-
	Tsukui	2018	5	5	0	0	0	0		4	1	0	4	0	0	0	ND	-	-	-	1	0	0	0	ND	-	-	-
	Total		17	13	3	0	1	0		14	3	0	12	1	0	1					1	2	0	0				
MTX-NS-LPD	Tokuhira	2018	9	8	1*	0	0	0	* PSL (poor PS)	8	1	0	8	1	0	0	Mean 67 (22-194)	-	-	-	0	1	0	0	-	24	-	-

EBV, Epstein-Barr virus; NR, not recorded; ND-LPD, non-distractive LPD; R, regressive group; R/R, relapse/regrowth group; P. persistent group; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; COPP, clophosphamide, vincristine, procarbazine, and prednisolone; PD, progressive disease; R-COP, rituximab, cyclophosphamide, vincristine and prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone.; C-MOPP, cyclophosphamide, vincristine, procarbazine, prednisolone; PD, progression disease; A, alive; D, dead.

markers for RRE; one such marker is decreased ACL in PB at the time of LPD development or RRE, as mentioned for LPD regression.[26-29] In our report, an ALC < 1000/μL at the time of LPD development is predictive of RRE.[30] Regarding other therapy options, several drugs, such as anti-PD-1 antibody and anti-CD30 antibody, can be applied for *de novo* CHL.[75,76] Eso *et al*. described a MTX-CHL patient with oral ulceration receiving rituximab, brentuximab vedotin (BV), and nivolumab during the clinical course.[75] The response was insufficient and the patient died due to disease progression. In another case report, Nakazato *et al*. reported a patient with RA-MTX-CHL who relapsed after ABVD administration, and she achieved complete response (CR) and remission of RA by BV administration as salvage therapy.[76] Other cases of MTX-CHL have been previously reported.[37,44,57,65,66,77-79] Rizz *et al*.[40] and Miranda *et al*.[80] also reviewed cases of CHL in OIIA-LPD.

MTX-P-LPD

B-LPD among IA-LPD usually exhibits EBV-related lesions, including hyperplasia, P-LPD, aggressive lymphomas, and rarely, indolent lymphomas.[1] The subtypes of PTLD, commonly EBV-mediated, are categorized into 3 types: ND-LPD, P-LPD, and M-LPD.[1] Although the former 2 subtypes are not clearly defined in OIIA-LPD, the subtypes of polymorphic/lymphoplasmacytic-LPD (the 2008 WHO classification)[1] or P/L-I (the 2017 WHO classification),[2] and HLL have consistent features with P-LPD.[1] To clarify this issue in OIIA-LPD, Kurita *et al*. proposed 3 categories of OIIA-LPD as defined for PTLD: reactive hyperplasia LPD (RH-LPD) as ND-LPD, P-LPD, and M-LPD.[15] In their analysis, P-LPD, consisting of P/L-I, HLL, and other p-LPD, accounted for 15% of 219 patients with MTX-LPD. The clinical data for P-MTX-LPD based on the previous reports are shown in Tables 3 and 4.[19,36,40,42,44,81-84] Among 17 patients with MTX-P-LPD, 11 and 6 were consistent with P-LPD and HLL, respectively. There were six male and 11 female patients. The mean age was 65 years, and all patients had RA. The mean duration of RA and MTX was 11 years and 7.2 years, respectively. Regarding tumor involvement, 41% of the patients had extranodal lesions, whereas 29% had localized lesions (Table 3). EBV positivity, based on EBER-1 staining, was 100% among 14 patients with P-LPD for whom EBER-1 staining was performed. Thirteen of the 17 MTX-P-LPD patients (76%) were in R-G, whereas 3 patients and 1 patient were in R/R-G and Ch-G, respectively (Table 4). Patients in R/R-G and Ch-G received ABVD and R-CHOP, respectively. The survival rate of the 17 patients with MTX-P-LPD was 82.3% (14/17). Among the patients with MTX-P-LPD, the patients with ulceration or localized mucosal lesions were categorized into EBVMCU, although the diagnosis was based on the original article in this list. The recommended chemotherapy for aggressive or relapsed P-LPD has yet to be defined, although some strategies, such as ABVD for HLL and R-CHOP for P-LPD, have been successful. Patients with MTX-P-LPD are also described in several reports.[57,85,86]

MTX-EBVMCU

EBVMCU is a newly recognized clinicopathological entity in the 2017 WHO classification occurring in elderly patients or due to ISD administration.[1] However, our understanding of this disease is limited because of its broad clinical and pathological features. Data for 32 cases of MTX-EBVMCU are presented in Table 5.[78,87-97] Twenty-seven female and five male patients were included. The mean age (70 years) was higher than that for other subtypes. Twenty-eight patients had RA, and they all had dermatomyositis, PM, Crohn's disease, and Sjögren's syndrome. The oral mucosa was the principal site, and cases involving the tongue, skin, eyelid, lip, nose, buccal mucosa, colon, rectum, or lung were also reported. Among 32 cases, 26 cases were in R-G, whereas 1 case, 4 cases, and 1 case were in R/R-G, P-G and Ch-G, respectively. Regarding chemotherapy, R-CHOP and ABVD were used for patients in P-G, and ABVD was used for patients in R/R-G (Table 5). The survival rate was 97% (31/32), but one patient died due to disease progression. Daroontum *et al*. reported a patient with MTX-EBVMCU who developed EBV+ P-LPD and EBV+DLBCL within 3 years.[95] Similar to MTX-P-LPD, chemotherapy for aggressive MTX-EBVMCU is decided according to the pathological features of M-LPD such as DLBCL and CHL. In this analysis, such chemotherapy was found to be effective for aggressive MTX-EBVMCU; however, whether the strategy of chemotherapy based on pathological features is suitable for MTX-EBVMCU requires further investigation. Other MTX-EBVMCU cases have been reported.[22,65,78,99-111] Sinit *et al*. reviewed 100 patients with EBVMCU separated by age, ISD, and primary/acquired immunodeficiency.[112]

MTX-ND / RH / non-specific (NS) - LPD

ND-LPD in PTLD is categorized into three subtypes, plasmacytic hyperplasia, infectious mononucleosis, and florid follicular hyperplasia.[1] In contrast, it is not defined for OIIA-LPD in the WHO classification, although it is common. Several cases of MTX-ND-LPD as RH or NS have been reported.[15,16,57] In our study, nine patients with MTX-NS-LPD were detected among 62 patients with MTX-LPD (14.5%), with the third highest incidence following DLBCL and CHL (Table 3).[16] The mean age was 65 years, and the AIDs included 8 cases of RA and 1 case of psoriasis vulgaris. The mean duration of RA and MTX administration was 16 years and 8.9 years, respectively. The CS of 6 patients was 1 or 2, and 3 patients had CS 4. Four of 7 (57%) patients were EBV+. Eight patients were categorized into R-G, whereas one patient who died due to EBV-LPD after RRE was categorized into R/R-G (Table 4). In our series, the median serum LDH, CRP, and sIL-2R in these 9 patients were 243 (range, 170-414) U/L, 2.0 (range, 0.3-9) mg/dL, and 1810 (range, 716-4510) U/L, respectively.[16] In a report by Kurita *et al*., all 28 MTX-RH-LPD patients with ND-LPD survived without chemotherapy, although 3 patients (11%) had stage IV disease.[15]

Regarding the management of MTX-ND/RH/NS-LPD,

Table 5. Clinical features and outcome of Epsiten-Barr virus-positive mucocutaneous ulcer (EBVMCU).

Subtype	Author	Year	N	Sex		Age		Basal disease				MTX duration		Tumor sites					Pattern				LPD therapy	Alive / Dead		OS (M)		Ref
								Types		Duration																		
				M	F	Mean	Range	RA	Other	Mean	Range	Mean	Range	oral	skin	tongue	eyelid	other	R	R/R	P	Ch		A	D	Mean	Range	
MTX-EBVMCU	Satoh	2009	1	0	1	73	-	1	-	NR		5	-	0	0	0	0	Gastric	1	0	0	0		1	0	8	-	87
	Dojcinov	2010	1	0	1	80	-	1	-	NR		NR		0	1	0	0		1	0	0	0		2	0	60	-	78
	Attard	2012	1	0	1	81	-	1		NR		NR		1	0	0	0		1	0	0	0		1	0	12	-	88
	Hashizume	2012	1	0	1	62	-	0	DM 1	NR		7	-	0	0	0	1	(+Lip, Nose)	1	0	0	0		1	0	1	-	89
	Yamakawa	2014	5	0	5	63	56-76	4	PM 1	NR		4.8	0.3-10	0	2	0	2	Bucca Mucosa	4	0	0	1*	* R-CHOP	4	0	24	1-37	42
	Sadasivam	2014	1	0	1	66	-	1		NR		NR		1	0	0	0		1	0	0	0		1	0	19	-	90
	Moran	2015	1	0	1	53	-	0	CD 1	NR		1	-	0	0	0	0	Colon, Rectum	0	1*	0	0	* ABVD	1	0	24	-	91
	Hashimoto	2015	2	0	2	74	74, 74	2	-	3.2	0.5, 6	2.7	0.5, 5	1	0	1	0		2	0	0	0		2	0	30	12-48	92
	Nakauyaca	2016	1	0	1	67	-	1	-	20	-	20	-	0	0	1	0		0	0	1*	0	* No therapy due to death	0	1	0	-	93
	Chen	2017	1	0	1	58	-	1	-	NR		NR		1	0	0	0		1	0	0	0		1	0	9	-	94
	Furudate	2017	1	1	0	74	-	1	-	NR		7	-	1	0	0	0		1	0	0	0		1	0	24	-	95
	Daroontum	2018	7	0	7	75	61-85	6	SjS 1	10	2-22	4	2-10	4	2	1	0		6	0	1*	0	* R-CHOP	7	0	40	31-81	96
	Satou	2018	9	4	5	72	48-87	9	-	NR		8.3	4-19	8	0	1	0		7	0	2*	0	* R-CHOP, ABVD	9	0	45	8-139	97
Total			32	5	27	70		28	4	9.4		6.3		17	5	4	3	3	26	1	4	1		31	1	32		

ND, not described; RA, rheumatoid arthritis; PM, polymyositis; PV, psoriasis vulgaris.
EBV, Epstein-Barr virus; ND, not described; DM, dermatomyositis; PM, polymyositis; CD, Crohn disease; R, regressive group; R/R, relapse/regrowth group; P. persistent group; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; A, alive; D, dead: OS ,overall survival; Ref, reference.

WW is useful because the major clinical course of this subtype is R-G. Similar to P-LPD, the strategy for patients with aggressive or relapsed MTX-ND/RH/NS-LPD is not defined. In previous reports, a number of other cases were demonstrated to be MTX-LPD.[110-125] We treated several patients with MTX-ND-LPD that changed to CHL during the clinical course; one patient developed severe EBV infection, and 2 diagnosed with ND-MTX-LPD developed CHL during WW.[126] The remaining issues, such as the definition of this category and management of aggressive MTX-ND/RH/NS-LPD, along with other issues specific to each type of MTX-LPD require further investigation.

Other MTX-LPD

Several other subtypes of MTX-LPD, including low grade B cell lymphomas, such as follicular lymphoma (FL),[1,2,19,57,65,71] mucosa-associated lymphoid tissue (MALT) lymphoma,[1,2,19,36,57,65,66,71,127-129] Burkitt lymphoma (BL),[1,2,57,130] intravascular lymphoma (IVL),[131,132] lymphoplasmacytic lymphoma,[65] plasmablastic lymphoma,[19,71] adult T-cell leukemia/lymphoma (ATLL),[133] angioimmunoblastic T-cell lymphoma (AITL),[1,2,134,135] anaplastic large cell lymphoma,[1,2,65,136,137] subcutaneous panniculitis-like T-cell lymphoma (SPLTCL),[138] peripheral T-cell lymphoma (PLCL),[1,2,19,36,37,57,139-141] and extranodal natural killer/T (NK/T)-cell lymphoma,[1,2,66,71,142-144] have been reported. Their clinical patterns vary. Regressive LPD after MTX withdrawal develops in FL, MALT lymphoma, ATLL, NK/T-cell lymphoma, SPLTCL, and PLTL, whereas some diseases relapse. In contrast, some patients with BL, IVL, or NK/T-cell lymphoma were classified into P-G. EBV was detected in MTX-low-grade lymphomas, which is commonly negative in *de novo* low-grade lymphomas. For example, EBV + FL[1] and MALT lymphoma cases in R-G that are EBV+ have been reported.[129] Regarding LPD regression, EBV-negative LPD, including NK/T-lymphoma and PTCL, also have a regressive phase.[66,141] Due to the small number of patients and the limited information on each subtype, assessment of optimal clinical management, such as WW or chemotherapy when LPD develops, requires further investigation in a larger patient population.

NON-MTX-LPD

A number of studies described non-MTX-LPD in comparison with MTX-LPD, although non-MTX-LPD-to-MTX-LPD ratios vary.[23,24,57,65,66,71,128] For example, Yamada *et al*. reviewed the background of OIIA-B-LPD,[23] and described that 25% of OIIA-LPD is associated with non-MTX drugs. Ichikawa *et al*. reported 17 patients with non-MTX-associated LPD among 102 patients with OIIA-LPD.[57] Furthermore, it is well established that AIDs other than RA develop in LPD patients during ISD treatment.[145-153] In addition, many cases of AIDs in regressive LPD patients after the withdrawal of non-MTX ISDs have been reported, suggesting the immunosuppressive effects leading to LPD development.[81,154-161] The history of MTX administration should be carefully assessed in patients with non-MTX-LPD because RRE occurs within several years after the withdrawal of MTX, especially in patients with RA.

CLINICAL MTX-LPD

In clinical practice, symptoms resembling LPD, and laboratory data, such as fever, lymphadenopathy, respiratory symptoms, and increased serum LDH/CRP/sIL-2R levels, are not rare. These manifestations may also develop in the pathogeneses of viral infection and AID activity. As a first step, drug withdrawal is tentatively attempted when such manifestations develop, similar to MTX-LPD. In addition, tissue biopsy should be performed to confirm the diagnosis; however, biopsy may fail for patients with rapid LPD regression after MTX withdrawal.[44] We analyzed such patients as the clinical MTX-LPD (c-MTX-LPD) group, composed of suspicious-LPD and proven-LPD (Figure 3).[162] MTX was withdrawn at the time of suspicious-LPD, and some of those with suspicious-LPD developed MTX-LPD, as confirmed by tissue biopsy (proven-LPD). Among the 28 patients with c-MTX-LPD, 7 developed proven-LPD after suspicious-LPD regression, 6 of whom had CHL and one who had plasmablastic lymphoma. Four of the 7 patients with proven-LPD(+) died, whereas all patients with proven-LPD(-) survived. The clinical manifestations included fever, increased serum CRP (>5 mg/dL), and sIL-2R level >4000 U/L at the time of recurrence, resembling LPD symptoms, suggesting the development of proven-LPD.[162] Although the reason is unclear, the subtypes, including EBV+ DLBCL, DLBCL-NOS, P-LPD, and EBVMCU, did not develop under clinical management with prompt MTX withdrawal. As the incidence of R/R-G among these subtypes was low (Tables 2, 4, and 5), such LPD may include suspicious c-MTX-LPD.

Anti-AID therapy after the development of MTX-LPD

AID activity commonly flares within one year after AID withdrawal in R-G or after chemotherapy in R/R-G and P-G. Thus, safe ISD usage without inducing LPD after OIIA-LPD

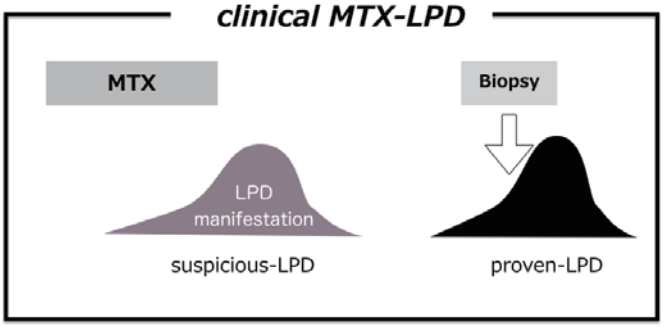

Fig. 3. Clinical methotrexate-associated lymphoproliferative disorders (c-MTX-LPD)[162]
Under MTX administration, MTX withdrawal is attempted when LPD or LPD-like manifestations occur (suspicious-LPD). However, MTX withdrawal often induces prompt regression of suspicious-LPD, making tissue biopsy impossible. After regression of suspicious-LPD, LPD occasionally recurs as relapse/regrowth event, resulting in the LPD diagnosis by tissue biopsy (proven-LPD).

development has been investigated. The guidelines of the American College of Rheumatology (2015) described several points regarding the usage of AIDs after OIIA-LPD development: very low quality evidence of ISD usage after OIIA-LPD, a possible increased risk of lymphoma associated with TNFi, and no evidence of increased risk by abatacept (ABT) or tocilizumab (TCZ).[163] The guidelines of the Japan College of Rheumatology state that ISDs should be avoided as much as possible, and MTX and TNFi are not generally recommended.[164,165] As many factors, such as type of AID, LPD subtype, ISD dose and duration, EBV activity, ALC in PB, and age, may be related to the development or relapse of OIIA-LPD, a complete understanding of AID usage after OIIA-LPD is difficult. In the analysis of c-MTX-LPD, seven ISDs, tacrolimus (FK), bucillamine (BUC), salazosulfapyridine (SSZ), infliximab (IFX), ABT, iguratimod (IGU), and adalimumab, were combined with MTX.[162] Thirteen types of ISDs were administered after suspicious-LPD, and 21 patients without proven-LPD received 12 ISDs, MTX, FK, BUC, SSZ, IFX, ABT, IGU, etanercept (ETN), golimumab, TCZ, certolizumab pegol, or tofacitinib, after suspicious-LPD regression. On the other hand, 7 patients with proven-LPD received FK, BUC, SSZ, or ETN, which were also administered to patients without proven-LPD. For patients with RA-MTX-LPD in CR, a difference between AIDs before and after MTX-LPD development was not observed.[162] From these data, it is difficult to identify the roles of specific ISDs in MTX-LPD development after MTX withdrawal.

PREDICTION OF MTX-LPD

Although the prediction of MTX-LPD is essential to prevent a poor prognosis due to AIDs, no concrete assessment is available. As mentioned earlier, a decrease in ALC in PB is one candidate, although this method is difficult to apply to P-G.[27,29] Based on the higher incidence of OIIA-LPD in Japan, several studies have focused on human leukocyte antigen (HLA) analysis. Yamakawa *et al*. analyzed 20 Japanese patients with MTX-LPD, and found that the allele B*15:11 is closely related to EBV infection.[42] Another HLA study on 25 patients with MTX-LPD identified 11 alleles, including A*2402 and DRB1*0405, that were significantly more commonly detected than in the general population.[16] However, data on HLA alleles are inconsistent between these two studies. Regarding PTLD, several studies suggested the possibility of prediction of LPD by measuring the EBV viral load;[166-169] however, standardization of the EBV assay and cut-off values for positive selection are of concern. Impairment due to EBV, as indicated by impaired T-cell response against EBV and increased EBV viral load after MTX administration, has been reported in patients with RA,[170-175] and several reports demonstrated the association between EBV viral road and disease activity in patients with juvenile idiopathic arthritis who developed MTX-LPD.[176] In contrast, several recent studies reported that the EBV viral load does not increase under the administration of ISDs such as MTX, TNFi, and ABT.[177-179]

SUMMARY

The data presented in this article are summarized in Table 6, and the specific features of MTX-LPD based on the previous data, including this review, are listed in Table 7. The proposal for clinical management of MTX-LPD is presented in Figure 4. When c-MTX-LPD develops, the first step is the withdrawal of MTX, in addition to differential diagnosis by annual health checks, laboratory investigations, such as serum LDH, CRP, sIL-2R levels, and other examinations for viral infections, basal disease activity, and other considered diseases. Imaging, including computer tomography and positron-emission tomography, is also used for the differential diagnosis. Examinations of bone marrow aspiration/biopsy and the measurement of EBV viral load are performed if necessary. To make a definite diagnosis of LPD, tissue biopsy is required at any time during the clinical course. After withdrawal of MTX, chemotherapy is administered to patients with non-regressive or aggressive LPD (P-G), whereas patients achieving complete response (CR) are followed-up without additional chemotherapy. When LPD relapses or recurs, chemotherapy is initiated (R/R-G). In contrast, the duration of WW is an important issue among patients with

Table 6. Summary of methotrexate associated lymphoproliferative disorders (MTX-LPDs)

MTX-LPD	N	Female (%)	Age* (y)	Basal disease* (y)	MTX duration* (y)	CS 3 or 4	EBV+ (%)	Clinical course (%)				Survival rate (%)				
								R-G	R/R-G	P-G	Ch-G	All	R-G	R/R-G	P-G	Ch-G
EBV+DLBCL	66	71	68	13.5	6.1	62	100	62	3	17	17	91	95	100	72	90
DLBCL-NOS	50	59	66	11.1	5.4	60	0	26	6	36	26	60	100	67	72	53
CHL	51	74	62	13	5.6	75	76	14	40	24	21	78	100	65	67	100
P-LPD	17	64	65	11	7.2	64	100	76	18	0	6	82	92	33	-	0
EBVMUCU	32	84	70	9.4	6.3	-**	100	81	3	13	3	97	100	100	75	100
NS-LPD	9	56	65	16	8.9	33	57	89	11	0	0	89	100	0	-	-
Total	225	70	66	12.5	6.1	54.7	70.6	48	13.5	20.3	16.4	81.3	97.2	67.7	67.2	81

EBV, Epstein-Barr virus; DLBCL, diffuse large B cell lymphoma; NOS, not otherwise specified; CHL, classical Hodgkin lymphoma; P-LPD, polymorphic LPD; EBVMCU, EEBV-positive mucocutaneous ulcer; CS, clinical stage; R-G, regression group; R/R-G, relapse/regrowth group; P-G, persistent group; Ch-G, chemotherapy group.
* indicated mean values. ** involved sites were mainly oral cavity and/or skin.

Table 7. Clinicopathological features of methotrexate-associated lymphoproliferative disorders (MTX-LPDs)

1. General features
- autoimmune disease (majority; rheumatoid arthritis)
- female dominant
- 5-10-times higher incidence in Japan
- median age: 65-70 years at the development of LPD
- basal disease duration:10-15 years
- MTX duration: 5-10 years
2. Pathological features
- MTX-LPDs from numerous cell origins such as B, T, and NK cells
- classified into ND/RH/NS-LPD, P-LPD, and M-LPD
- P-LPD: HLL and P/L-I
- EBVMCU also develops
- major M-LPD; DLBCL (30-40%) and CHL (10-20%)
- EBV positivity in CHL: 70-80%
3. Clinical features
- clinical state 3 or 4: over 50% of MTX-LPD
- LPD regression after MTX: 50-70%
- three clinical patterns after LPD regression with MTX withdrawal: R-G, R/R-G, and P-G
- LPD regression: related to recovery of lymphocytes in peripheral blood (PB)
- population of lymphocytes in PB: CD8+T cells and NK cells
- lower rate of DLBCL and higher rate of CHL in R/R-G
- aggressive LPD is also seen in ND/RH/NS-LPD, P-LPD, and EBVMCU
4. Prognosis
- OS of MTX-LPD: 70-85% survived
- R-G and EBVMUC: better OS
- elderly (>70 years): poor OS
5. Others
- usage of ISDs after LPD development: under investigation
- prediction of LPD development: under investigation for ALC in PB, HLA alleles, and EBV viral load.

NK, natural killer; ND, non-destructive; RH, reactive hyperplasia; NS, non-specific; P-LPD, polymorphic LPD; M-LPD, monomorphic LPD; HLL, Hodgkin-like lesions; P/L-I; polymorphic/lymphoplasmacytic infiltrates; EBVMCU; Epstein-Barr virus-positive mucocutaneous ulcer; DLBCL, diffuse large B cell lymphoma; CHL, classical Hodgkin lymphoma; R-G, regressive group; R/R-G, relapse/regrowth group; P-G. persistent group; ISD, immunosuppressive drug; ALC, absolute lymphocyte count; HLA, human leukocyte antigen.

residual tumor burden under LPD regression. The management of patients with responses less than CR state after MTX withdrawal is dependent on the physician's decision whether chemotherapy is required under such situation. In our report, the recovered ALC in PB lasted for at least 2 years in patients with MTX-LPD in R-G, and it gradually decreased after 6 months of MTX withdrawal toward RRE in R/R-G.[30] Because the pathogenesis of LPD regression is complexed on the basis of various factors, including LPD subtypes, LDP tumor burden, EBV activation, types or combination of ISDs, and ALC in PB, the definite answer for the duration of WW is not concluded yet. Regarding non-MTX-LPD, the patient accumulation is required to conclude the precious assessment, although the management of non-MTX-LPD might be based on that of MTX-LPD.

The pathogenesis of MTX-LPD and related factors are illustrated in Figure 5. Impairment by EBV, the chronic inflammation process in AIDs, immune abnormality, including genetic background, such as HLA restriction, and aging may underlie IA-LPD. ISD administration accelerates the impairment of anti-LPD immunity, and consequently, LPD develops. The duration between ISD administration and LPD development ranges widely from a few months to over 30 years; therefore, triggers, including a decrease in ALC in PB, may occur at the time of LPD development. After ISD withdrawal, LPD regresses in R-G and R/R-G, but not in P-G. Lymphocytes, such as CD8+ T cells and NK cells, play important roles in LPD regression. When ISDs are administered for AID activity after LPD development, no RRE occurs if the potent immunity against LPD remains (R-G), whereas loosing anti-LPD immunity is categorized in R/R-G. After MTX-LPD development, several factors, such as the subtypes of MTX-LPD, decrease in ALC in PB, EBV reactivation, and impairment of anti-LPD immunity mediated by ISDs, may influence RRE. Although the disease entity of MTX-LPD is still controversial, the phenomenon of regression after withdrawing ISDs suggests the direct influence of MTX on LPD development. MTX-LPD is an important adverse event in AIDs, resulting in a poor outcome.

On the other hand, many ISDs, including MTX and TNFi, have significantly improved the quality of life and OS of patients with AIDs, especially RA. To establish a safe AIDs treatment for patients developing MTX-LPD, issues, such as a standard therapy for each subtype of MTX-LPD, the validation of predictive factors, including ALC, HLA alleles, EBV viral load, and the estimation of OS under

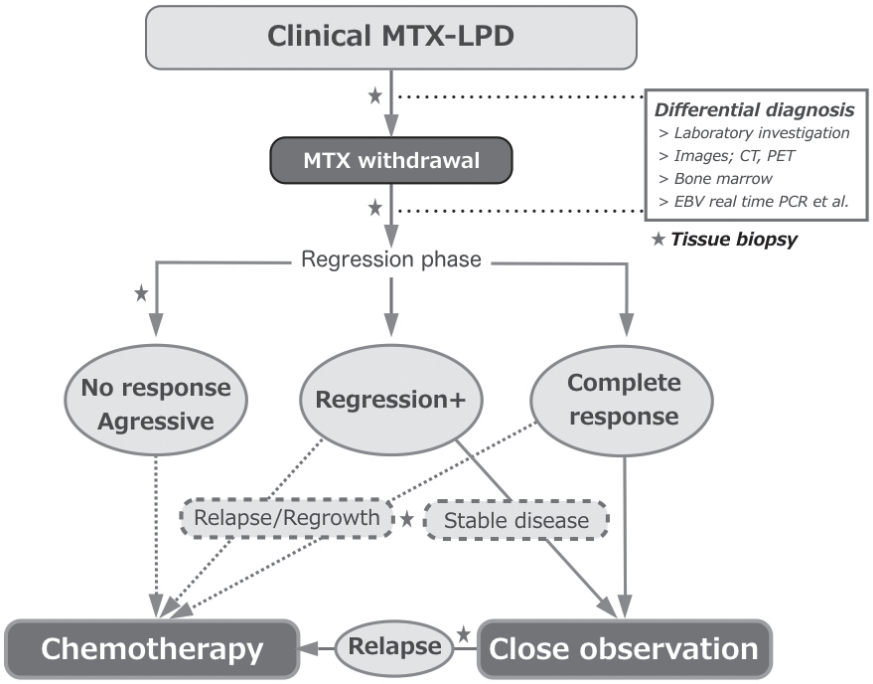

Fig. 4. Clinical management of methotrexate-associated lymphoproliferative disorders (MTX-LPD)
When clinical-MTX-LPD develops, MTX withdrawal is the first procedure. In addition to watchful waiting, the differential diagnosis is performed by laboratory investigation and imaging. Bone marrow aspiration/biopsy and the measurement of EBV viral load are considered according to the patient's clinicopathogenesis. To diagnose LPD, tissue biopsy is required at any time during the clinical course. After MTX withdrawal, chemotherapy is considered for patients with non-regressive LPD or aggressive LPD, and relapse/regrowth after the regressive phase. Among patients with residual LPD under LPD regression, the decision for chemotherapy is based on the physician's assessment.

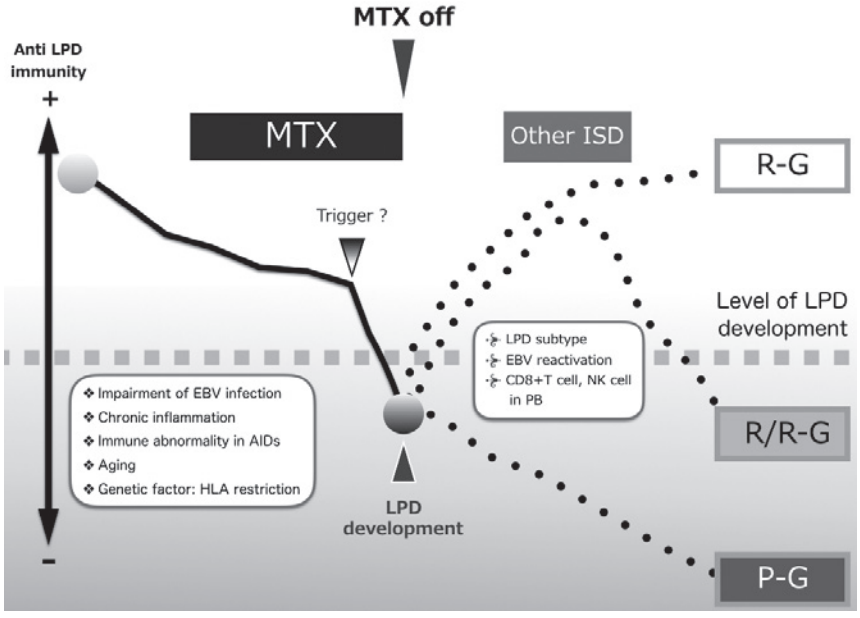

Fig. 5. Pathogenesis of methotrexate-associated lymphoproliferative disorders (MTX-LPD)
Regarding the development of MTX-LPD, impairment by EBV, the chronic inflammation process in autoimmune diseases (AIDs), immune abnormality in AIDs, including genetic background, such as human leukocyte antigen (HLA) restriction, may be underlying factors. Immune suppressive drugs (ISDs), including methotrexate (MTX), accelerate the impairment of anti-LPD immunity, and consequently, LPD develops. Triggers, including a decrease in the absolute lymphocyte count (ALC) in peripheral blood (PB), may occur at the time of LPD development. After ISD withdrawal, LPD regression occurs in the regressive group (R-G) and relapse/regrowth group (R/R-G), but not in the persistent group (P-G). Lymphocytes, such as CD8+ T cells and natural killer (NK) cells, play important roles in LPD regression. When ISDs are administered for AID activity after LPD development, no relapse/regrowth event (RRE) occurs if the potent immunity against LPD remains (R-G), whereas the loss of anti-LPD immunity is categorized in R/R-G. After MTX-LPD development, several factors, such as the subtypes of MTX-LPD, decrease in ALC in PB, EBV reactivation, and impairment of anti-LPD immunity mediated by ISDs, may influence RRE.

long-term observation, need to be assessed to discriminate among MTX-LPD subtypes. In addition, the clinical assessment of non-MTX-LPD is another important issue in OIIA-LPD. As several clinical questions regarding OIIA-LPD, such as whether the management of non-MTX-LPD is similar to that of MTX-LPD, remain, further analyses will be performed for their clarification.

CONFLICT OF INTEREST

TJ received honoraria from Takeda Pharmaceutical Company Limited. The remaining authors declare no competing financial interests.

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