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Original Article

The 3q27 and 18q21 Translocations for Follicular Lymphoma and Diffuse Large B-Cell Lymphoma in the Rituximab Era

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The 3q27 and 18q21 chromosomal translocations are major hallmarks in B-cell lymphoma. We aimed to determine the frequencies of these translocations in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) and to evaluate their prognostic impact in the rituximab era. This study included 98 FL and 93 DLBCL patients whose abnormal karyotypes had been detected using G-banding. Patients uniformly underwent R-CHOP therapy : doxorubicin, cyclophosphamide, vincristine, prednisolone, and rituximab ; survivors were followed up for 29 months (median). The 3q27 and 18q21 translocations were detected in 14 and 77 FL patients and 14 and 22 DLBCL patients, respectively. Overall survival (OS) and progression-free survival (PFS) did not differ significantly between the groups with 3q27, 18q21, concurrent 3q27 and 18q21 translocations, and other chromosomal abnormalities for FL and DLBCL. There were no significant differences in OS and PFS between patients with 3q27 translocation-positive FL and those with 3q27 translocation-positive DLBCL or between the patients with 18q21 translocation-positive FL and those with 18q21 translocation-positive DLBCL. The presence of 3q27 and 18q21 translocations did not correlate with the clinical outcomes of FL or DLBCL patients following R-CHOP treatment. 〔*J Clin Exp Hematop 53(2) : 107-114, 2013*〕

Keywords: 3q27 translocation, 18q21 translocation, follicular lymphoma, diffuse large B-cell lymphoma, prognosis

INTRODUCTION

Clonal chromosomal abnormalities are associated with but not always specific for histologically distinct non-Hodgkin's lymphomas (NHL). Cytogenetic and molecular studies of NHL have revealed the presence of recurrent chromosomal translocations involving *BCL2* and *BCL6*. Generally, these chromosomal alterations involve immunoglobulin (Ig) gene loci as partners, resulting in oncogenic deregulation of gene expression under the influence of the juxtaposed Ig regulatory sequences.

BCL2, localized mainly to the inner mitochondrial membrane, counteracts apoptosis.[1] *BCL2* was originally discovered owing to its involvement in the t(14;18)(q32;q21) translocation,[2] which juxtaposes *BCL2* from 18q21 to the Ig heavy chain locus, resulting in BCL2 overexpression.[3] This leads to interference with programmed cell death independent of the promotion of cell division.[1] *BCL2* rearrangement has been observed in 70-95% of follicular lymphomas (FLs)[4,5] and 20-30% of diffuse large B-cell lymphomas (DLBCLs).[6,7]

The *BCL6* proto-oncogene was identified by virtue of its involvement in chromosomal translocations affecting band 3q27 in NHL.[8,9] *BCL6* encodes a 96-kDa sequence-specific transcriptional repressor characterized by 6 C-terminal zinc finger motifs and an N-terminal POZ/ZIN domain similar to those of the family of zinc finger proteins.[8] Several studies have suggested that relieving normally downregulated BCL6

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expression levels might promote differentiation arrest, continuous cell proliferation, survival, and genetic instability, all of which could lead ultimately to neoplastic transformation.[10] Germinal center (GC) formation requires BCL6 activity,[11] the expression of which is strictly regulated during B-cell ontogeny. Thus, it is almost exclusively expressed in GC lymphocytes or lymphomas originating at the GC differentiation stage.[12] *BCL6* rearrangement was observed in 30-35% of DLBCLs and 10-15% of FLs.[13-15]

The prognostic utility of these translocations in FL and DLBCL is controversial. In FL, in the pre-rituximab era, one study related the presence of the t(14;18) translocation to clinical outcome,[16] although others did not demonstrate its prognostic significance.[17,18] It has been suggested that some recurring additional abnormalities have a prognostic impact.[17] FL with *BCL6* rearrangements in the absence of the t(14;18) translocation has rarely been reported,[19] and one study based on a small number of cases showed it had no effect on clinical outcomes.[15]

Regarding DLBCL in the pre-rituximab era, some studies have shown that the presence of *BCL2*[20-22] and *BCL6*[15,22] rearrangements had no effect on prognosis, whereas, in contrast, others[23,24] have demonstrated better outcomes in patients with *BCL6* rearrangement. In contrast, BCL2 expression was an independent unfavorable risk factor for DLBCL patients' clinical outcome, although there was almost no correlation between *BCL2* rearrangement and BCL2 expression.[22]

Since the introduction of R-CHOP therapy (doxorubicin, cyclophosphamide, vincristine, prednisolone, and rituximab), the prognostic significance remains uncertain. In DLBCL, Barrans *et al*.[25] revealed that the presence of *BCL2* or *BCL6* rearrangement by fluorescent *in situ* hybridization was not prognostically significant in the era of R-CHOP treatment. There are limited prognostic data for FL and DLBCL with respect to *BCL2* or *BCL6* rearrangements in the R-era, and no study, to our knowledge, has compared FL and DLBCL patients treated uniformly with R-CHOP. We therefore set out to determine the frequency of the 3q27 and 18q21 translocations in FL and DLBCL and to evaluate their prognostic impact in the R-era using the G-banding method.

MATERIALS AND METHODS

Of 2,122 consecutive patients with untreated malignant lymphoma seen by the Yokohama City University Hematology group during the period from January 2001 through October 2009, 330 and 937 patients were diagnosed, respectively, with FL and DLBCL, according to the WHO classification.[26] One hundred and forty FL and 152 DLBCL patients had abnormal karyotypes that had been detected using G-banding at diagnosis. Among them, 98 FL and 93 DLBCL patients who received R-CHOP therapy were the subjects of this study. Other large B-cell lymphomas including primary mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, and primary effusion lymphoma were excluded using published diagnostic criteria.[26] CD5-positive DLBCL and Epstein-Barr virus-positive DLBCL were not excluded from this study cohort. All eligible newly diagnosed FL patients, except for Ann Arbor stage I and DLBCL patients at any stage, were treated with 6-8 cycles of R-CHOP therapy every 3 weeks. The median follow-up period was 29 months for surviving patients. Yokohama City University Hospital's ethics committees approved this study.

Overall survival (OS) was calculated from the beginning of treatment to the date of death from any cause or last contact. Progression-free survival (PFS) was calculated from the beginning of treatment to the date of disease progression, death from any cause, or last contact, whichever occurred first. Survival was estimated from Kaplan-Meier curves and compared using the log-rank test. $P < 0.05$ was considered to indicate statistical significance. Differences between groups were evaluated by the χ^2 test (nonparametric analysis). All statistical analyses were performed with SPSS Ver. 19.

RESULTS

Patients' characteristics

Patients' characteristics are summarized in Table 1. Their median age was 61 years (range : 19-89 years), and the male-to-female ratio was 1.08:1. Serum lactate dehydrogenase level was elevated in 37 (38%) FL patients and 59 (63%) DLBCL patients. B symptoms were present in 6% and 37% of cases, bulky mass in 22% and 14%, and bone marrow (BM) involvement in 52% and 34% for FL and DLBCL patients, respectively. Fifty-nine patients (31%) presented with international prognostic index low, 49 (26%) low-intermediate, 45 (24%) high-intermediate, and 38 (20%) high for the entire cohort. The 98 FLs were classified as histological grade 1 (n = 36 ; 37%), grade 2 (n = 40 ; 41%), grade 3 a (n = 12 ; 12%), grade 3b (n = 4 ; 4%), and unknown (n = 6 ; 6%) according to the WHO scheme.[26] FL grade 3b cases were included in the FL group.

FL and DLBCL patients' survival

The 3q27 and 18q21 translocations were detected in 14 and 77 FL cases and 14 and 22 DLBCL cases, respectively. Concurrent 3q27 and 18q21 translocations were observed in 7 of 98 patients with FL and in 1 of 93 DLBCL patients. In the 77 FL patients with 18q21 translocation, 72 patients presented with t(14;18)(q32;q21), 2 t(2;18)(p12;q21), 2 add(18)(q21), and 1 del(18q21). In the 22 DLBCL patients with 18q21 translocation, 16 patients presented with t(14;18)(q32;q21) and 6 with add(18)(q21). 8q24 translocation was observed in

Table 1. Characteristics of patients (n = 191)

Characteristics		FL (n = 98)	DLBCL (n = 93)
Age (years)	< 60	51	29
Median age 61 (19-89)	≧ 60	47	64
Gender	Male	48	51
	Female	50	42
Performance status	0,1	93	65
	2,3,4	5	28
Serum LDH level	Normal	61	34
	Elevated	37	59
B symptoms	Absent	92	59
	Present	6	34
Stages	I,II	16	36
	III,IV	82	57
Bulky mass	Absent	76	80
	Present	22	13
BM involvement	Absent	47	61
	Present	51	32
IPI	L	30	29
	L-I	36	13
	H-I	24	21
	H	8	30

FL, follicular lymphoma ; DLBCL, diffuse large B-cell lymphoma ; LDH, lactate dehydrogenase ; BM, bone marrow ; IPI, International Prognostic Index ; L, low risk ; L-I, low-intermediate risk ; H-I, high-intermediate risk ; H, high risk

7 of 93 DLBCL patients.

FL and DLBCL patients' OS and PFS values are shown in Fig. 1. FL patients' OS (log-rank test, $P = 0.005$) indicated significantly better prognoses than those of DLBCL patients. PFS was not significantly different between the FL and DLBCL patients.

FL and DLBCL patients' survival relative to 3q27 and 18q21 translocation and other chromosomal abnormalities

As shown in Table 2, the 98 FL patients could be divided into four groups and their clinical characteristics were compared as follows : patients with 3q27 translocation (n = 7), those with 18q21 translocation (n = 70), concurrent 3q27 and 18q21 translocations (n = 7), and those with other chromosomal abnormalities (n = 14). BM involvement was observed more frequently in patients with 18q21 translocation than among the other 3 groups ($P = 0.013$). Other characteristics did not differ significantly among groups. Comparison of OS and PFS according to the chromosomal abnormality showed no significant differences among the 4 groups (Fig. 2A & 2B). Regardless of the presence of 3q27 and 18q21 translocations, there were no significant differences in terms of OS and PFS (data not shown).

The 92 DLBCL patients were divided into the following three groups, and their clinical characteristics were compared (Table 3) as follows : patients with the 3q27 translocation (n = 13), or 18q21 translocation (n = 21), and those with other chromosomal abnormalities (n = 58). One patient with concurrent 3q27 and 18q21 translocations was excluded. There

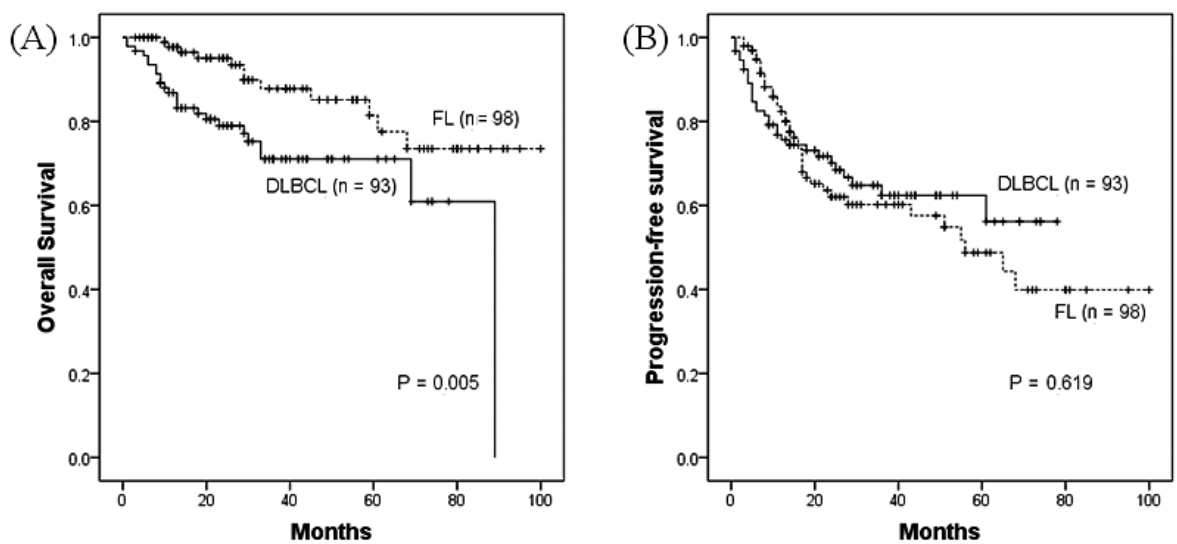

Fig. 1. Survival outcomes were compared between follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) patients. Overall survival (*1A*) was significantly better in FL than in DLBCL patients ($P = 0.005$). Progression-free survival (*1B*) did not differ between them.

Table 2. Comparison of patients with FL based on chromosomal abnormality (n = 98)

Characteristics		3q27 translocation (n = 7)	18q21 translocation (n = 70)	3q27 and 18q21 translocation (n = 7)	other abnormality (n = 14)	p-value
Age (years)	< 60	3	38	4	6	
	≧ 60	4	32	3	8	0.820
Gender	Male	4	30	4	10	
	Female	3	40	3	4	0.236
Performance status	0,1	7	66	7	13	
	2,3,4	0	4	0	1	0.819
Serum LDH level	Normal	5	46	3	7	
	Elevated	2	24	4	7	0.454
B symptoms	Absent	7	64	7	14	
	Present	0	6	0	0	0.465
Stages	I,II	2	8	1	5	
	III,IV	5	62	6	9	0.118
Bulky mass	Absent	6	53	7	10	
	Present	1	17	0	4	0.435
BM involvement	Absent	5	30	1	11	
	Present	2	40	6	3	0.013
IPI	L	3	22	2	3	
	L-I	2	24	2	8	
	H-I	2	18	2	2	
	H	0	6	1	1	0.886

FL, follicular lymphoma ; DLBCL, diffuse large B-cell lymphoma ; LDH, lactate dehydrogenase ; BM, bone marrow ; IPI, International Prognostic Index ; L, low risk ; L-I, low-intermediate risk ; H-I, high-intermediate risk ; H, high risk

were no significant differences among the 3 groups in terms of age, gender, performance status, serum lactate dehydrogenase level, B symptoms, stage, BM involvement, and international prognostic index. Bulky mass was present in 15% of 3q27 translocation cases, 33% of those with 18q21 translocation, and 7% of those with other abnormalities (P = 0.012). The 3 DLBCL patient groups' OS and PFS are shown in Fig. 2C & 2D. There were no significant differences in OS and PFS among the 3 groups. OS and PFS did not differ significantly according to the presence or absence of 3q27 and 18q21 translocations (data not shown).

3q27/18q21 translocation-positive FL and DLBCL patient survival rates

There were no significant differences in OS or PFS for 3q27 translocation-positive FL or 3q27 translocation-positive DLBCL patients. Specifically, the 3-year OS were 83.9% and 68.1%, respectively, among the patients with 3q27 translocation-positive FL or DLBCL (Fig. 3A). Their respective 3-year PFS were 46.2% and 62.3% (Fig. 3B).

The 3-year OS were 87.3% and 69.1%, respectively, for 18q21 translocation-positive FL and DLBCL (Fig. 3C). The 3-year PFS were 62.1% and 60.3%, respectively, among 18q21 translocation-positive FL and DLBCL (Fig. 3D).

DISCUSSION

In the present study, there were no significant differences in OS and PFS according to the presence of 3q27 and 18q21 translocations detected by G-banding in R-CHOP-treated FL and DLBCL patients. From these results, we conclude that the prognoses of FL and DLBCL patients' harboring 3q27 or 18q21 translocations who received R-CHOP therapy were the same as for those without the translocations. Barrans *et al*.[25] investigated *BCL2*, *BCL6*, and *MYC* rearrangement using fluorescent *in situ* hybridization and reported that *BCL2* and *BCL6* rearrangement did not correlate with R-CHOP-treated DLBCL patients' prognoses. In our study cohort, 8q24 translocation was observed in 7 patients with DLBCL, and OS and PFS were significantly lower in DLBCL patients with 8q24 translocation than in those without it (data not shown). Other chromosomal abnormalities[27] or translocation partners[28] were reported to provide prognostic significance during the pre-rituximab era, but the small number of eligible cases in our study limits any meaningful analysis. Interestingly, our data showed no significant differences in OS and PFS between the 3q27 translocation-positive FL and 3q27 translocation-positive DLBCL, and 18q21 translocation-positive FL and 18q21 translocation-positive DLBCL, although DLBCL patients' OS was significantly lower than that of FL patients.

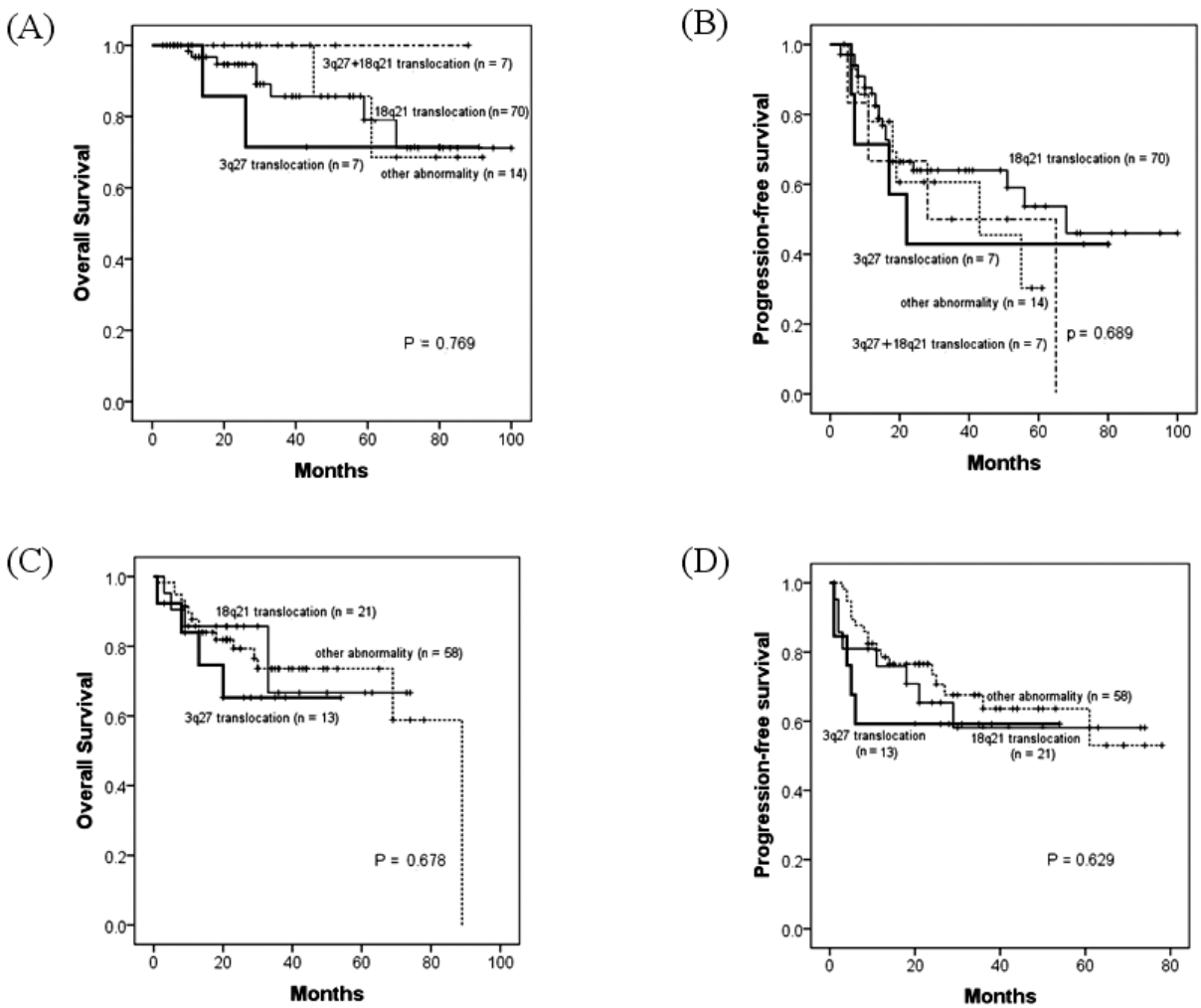

Fig. 2. Comparison of survival outcomes in patients with follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) based on chromosomal aberrations. There were no significant differences in FL overall survival (OS)(*2A*) and progression-free survival (PFS)(*2B*) among the following 4 groups : 3q27 translocation, 18q21 translocation, 3q27 + 18q21 translocation, and other abnormalities. DLBCL OS (*2C*) and PFS (*2D*) did not differ between the 3q27 translocation, 18q21 translocation, and other abnormality groups.

These findings suggest that there is another factor responsible for DLBCL's lower OS. We speculate that the 8q24 translocation in DLBCL might be an etiological factor.

Chromosomal translocation has been reported to contribute to the pathogenesis and biologic features of malignant lymphoma.[29,30] In our study, BM involvement was observed more frequently in FL patients with 18q21 translocation than in those without it. In DLBCL, 18q21 translocation-positive patients have a bulky mass more frequently. Thus, 18q21 translocation was associated with specific tumor characteristics in FL and DLBCL.

We show here that 3q27 and 18q21 translocation frequencies in FL patients were 14% and 79%, respectively, and the frequency of 18q21 translocations in DLBCL patients was 24%. These results are consistent with those reported previously.[4-7,13,15] In contrast, 3q27 translocation was observed in 15% of DLBCL patients, a value lower than that reported elsewhere.[13-15] This may due to the sensitivity of G-banding to detect recurrent chromosomal rearrangements, which is lower than that of molecular methods. The application of different molecular techniques for assessing the rearrangements was one of the reasons for the differences of previous results for prognostic impact of *BCL2* and *BCL6* rearrangements. The results by G-banding were only obtained from the cases able to reach metaphase. Additional limitations are that G-banding cannot distinguish 18q21.3/*BCL2* translocation found in FL from 18q21.1/*MALT1* translocation found in a subset of extranodal marginal zone lymphomas of mucosa-associated type. However, only G-banding can evaluate the entire karyotype and identify

Table 3. Comparison of patients with DLBCL based on chromosomal abnormality (n = 92)

Characteristics		3q27 translocation (n = 13)	18q21 translocation (n = 21)	other abnormality (n = 58)	p-value
Age (years)	<60	3	9	17	
	≧ 60	10	12	41	0.404
Gender	Male	9	12	30	
	Female	4	9	28	0.509
Performance status	0,1	8	17	39	
	2,3,4	5	4	19	0.401
Serum LDH level	Normal	4	6	24	
	Elevated	9	15	34	0.513
B symptoms	Absent	8	14	36	
	Present	5	7	22	0.926
Stages	I,II	6	8	21	
	III,IV	7	13	37	0.800
Bulky mass	Absent	11	14	54	
	Present	2	7	4	0.012
BM involvement	Absent	9	12	39	
	Present	4	9	19	0.670
IPI	L	3	9	17	
	L-I	3	0	9	
	H-I	3	5	13	
	H	4	7	19	0.508

FL, follicular lymphoma ; DLBCL, diffuse large B-cell lymphoma ; LDH, lactate dehydrogenase ; BM, bone marrow ; IPI, International Prognostic Index ; L, low risk ; L-I, low-intermediate risk ; H-I, high-intermediate risk ; H, high risk

abnormalities including translocation partner and additional chromosomal abnormalities that may have prognostic significance.

In conclusion, there was no statistically significant correlation between the presence or absence of the 3q27 and 18q21 translocations and FL and DLBCL patients' clinical outcomes in the R-era. Moreover, 3q27 translocation-positive FL and DLBCL, and 18q21 translocation-positive FL and DLBCL patients receiving R-CHOP therapy showed similar outcomes. However, long-term observations are needed to validate these findings.

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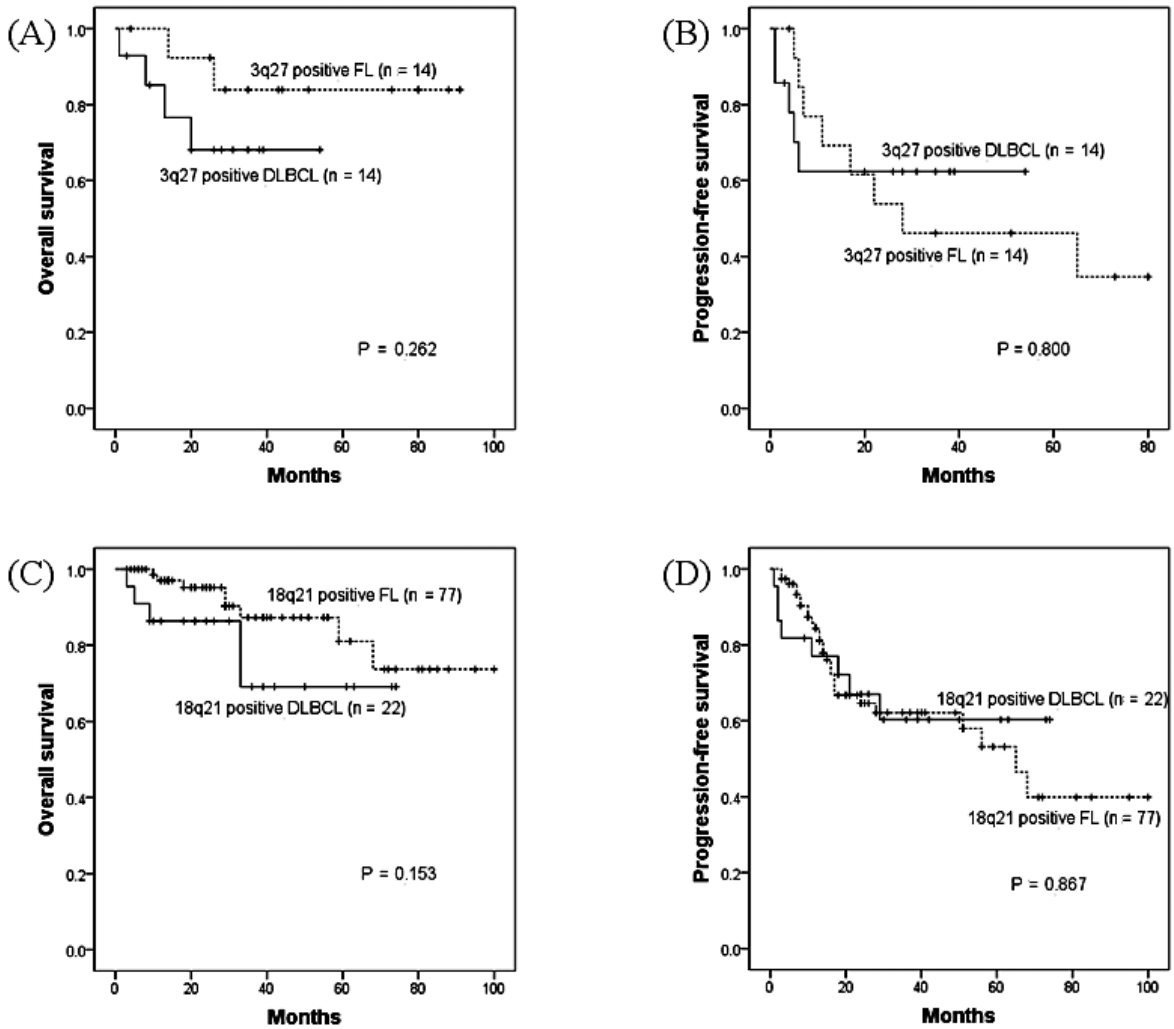

Fig. 3. Comparison of overall survival (OS) and progression-free survival (PFS) between the translocation-positive follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) cases. OS (*3A*) and PFS (*3B*) were not different in FL and DLBCL patients with the 3q27 translocation. OS (*3C*) and PFS (*3D*) also did not differ significantly between FL and DLBCL patients with the 18q21 translocation.

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