의학석사 학위논문

소포성 림프종의 임상적 및 병리학적 특징과 FISH 분석을 통한 세포유전학 특징의 분석에 대한 연구

Clinicopathologic and cytogenetic fluorescence in situ hybridization analysis study of follicular lymphoma

울 산 대 학 교 대 학 원

의 학 과

김 미 정

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이 논문을 의학석사 학위 논문으로 제출함

2020 년 2 월

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김 미 정

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Abstract

Background

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma in western countries, but is relatively rare in Asia. Only a few studies have described its genetic aberration and clinicopathologic significance in Asia.

Methods

We retrospectively analyzed annual frequency of FL and clinicopathological features of 296 cases of FL between 1991 and 2017. We applied fluorescence in situ hybridization (FISH) analysis to investigate prognostic significance of BCL2, BCL6, and MYC translocation or copy number aberration (CNA) in 129 FL cases between 2013 and 2017 in Asan Medical Center in Seoul.

Results

The annual frequency of FL (patients with FL/total inpatients) has increased from 0.01% in 1991 to 0.04% in 2017. Patients predominantly belonged to low risk group of FLIPI and low histologic grade. 7.2% of patients showed diffuse large B-cell lymphoma (DLBCL) transformation. Majority of patients (63.7%) was treated with chemotherapy (25.5%, R-CHOP; 21.7%, R-CVP). Of the histologic parameters, higher grade was associated with less frequent expression of BCL6 or CD10 ($P<0.05$ and $P<0.001$, respectively). Ki-67 index showed significant correlation with grade ($p<0.001$) and growth pattern ($p<0.001$). High risk group of FLIPI and FL grade 3B showed worse OS ($P<0.001$ and $P=0.002$, respectively). By FISH analysis, higher grade showed lower frequency of BCL2 translocation ($P < 0.001$). By univariate analysis, BCL6 CNA showed correlation with worse OS and PFS, while BCL2 CNA and MYC CNA did not (HR, 11.884; 95% CI, 1.170 – 120.756, $P = 0.036$).

Conclusions

This study shows recent increase in incidence, clinicopathologic and cytogenetic characteristics of FL in Korea. Of the cytogenetic features, FL with CNA of BCL6 was significantly associated with poor survival outcome. This study is the first report to evaluate prognostic significance in clinicopathologic and cytogenetic factors including CNA of BCL2, BCL6 and MYC in Korea population.

Keywords: translocation, copy number aberration, follicular lymphoma, pathology

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Introduction

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL) accounting for 20% to 35% of NHL in western countries [1)]. In Asia, by the '90s, the incidence was relatively low, approximately 5% to 10% of NHL [2-4)]. Recently, the rate has rapidly increased and FL is the second most common low-grade B-cell lymphoma after mucosa-associated lymphoid tissue (MALT) lymphoma in Asia [3, 5-7)]. It is still rarer than in western countries, and this may reflect differences of ethnic background including genetic and environmental factors.

FL affects predominantly adults, with a median age in the sixth decade of life and no sex predominance. It usually involves lymph node, but extranodal sites (bone marrow, gastrointestinal tract, soft tissue, and breast, etc.) can be affected. Transformation occurs in 25% to 35% of patients, most frequently to diffuse large B-cell lymphoma [8)].

FL is a neoplasm of follicular center B-cells. Histologically, FL shows effacement of normal lymph node architecture by back-to-back neoplastic follicles. Histologic grade is based on the number of centroblasts per high-power field (HPF), and it is associated with clinical outcome. With current therapies, FL grade 1-2 (FL1-2) and FL grade 3A (FL 3A) show favorable outcome with median survival, > 12 years, while FL grade 3B (FL 3B) shows worse prognosis [1, 9)].

Immunophenotypically, FL typically shows coexpression of CD10, BCL6, and BCL2 within the follicles. A chromosomal translocation, t(14;18)(q32;q21) is the genetic hallmark of FL (85–90% of nodal FL cases). However, approximately 15% to 30% of FL 3B show lack of BCL2 translocation [8, 10)]. BCL6 translocation has been reported at a lower frequency in FL (13% or 14.3%) [11, 12)]. It is more

frequently found in FL 3B at a frequency of 44% and t(14;18)-negative FL at a frequency of 22% [11, 13]. In addition to translocation, copy number of BCL6 has been shown to be increased in FL 3A or FL 3B [14]. However, the prognostic significances of extra copies in BCL2, BCL6, or MYC gene have not been fully studied.

In Korea, despite the increased incidence of FL, only a few clinicopathological studies have been described. In this study, we analyzed clinicopathologic characteristics of FL in Korea. In addition, using fluorescence in situ hybridization (FISH) analysis, we studied BCL2, BCL6, and MYC translocation, and copy number status, and evaluated their clinicopathologic relevance and prognostic significance.

Materials and methods

Clinicopathologic analysis

As a retrospective study, a total of 296 FL cases (296 patients) which was diagnosed between 1991 and 2017 in the Asan Medical Center in Seoul, were included. Only excisional biopsy cases were involved. To analyze annual frequency of FL between 1991 and 2017, we used Asan BiomedicaL research Environment (ABLE), which is clinical database system of the institution. Annual proportion of patients with FL to total inpatients between 1991 and 2017, and annual proportion of FL cases to all lymphoid malignancies between 2007 and 2017 were measured [15, 16)]

As for clinicopathologic parameter, the following features were evaluated for all specimen using medical records: patient demographic data (age and sex), presence or absence of B symptoms (fever, night sweats, and weight loss), high grade transformation, results of complete blood count, lactate dehydrogenase (LDH) level, bone marrow biopsy, extra-nodal involvement, Ann-Arbor stage, treatment modalities, and FLIPI risk groups; as for pathologic parameters, histologic grade (FL 1-2, FL 3A, FL3B), growth pattern (follicular, follicular and diffuse, diffuse pattern), and immunophenotypes (BCL2, BCL6, CD10) were evaluated.

Fluorescence in situ hybridization (FISH) analysis

Of all 296 cases analyze for clinicopathologic characteristics, 129 cases were included for FISH analysis of BCL2, BCL6, and MYC, which were diagnosed between 2013 and 2017. Tissue microarrays (2mm x 3 cores per cases) were made from formalin-fixed, paraffin embedded tissue blocks. The following

probes were used to evaluate BCL2, BCL6, and MYC translocation or copy number status: LSI BCL2 (18q21) Dual Color, Break Apart Rearrangement Probe (Vysis), LSI BCL6 Dual Color, Break Apart Rearrangement Probe (Vysis), and LSI MYC Dual Color, Break Apart Rearrangement Probe (Vysis). Case was considered as translocation if more than 10% of 60 nuclei had split signals with at least two signal width apart in tumor cells [17]. Case was considered as copy number aberration (CNA) if ≥5% of 200 nuclei had extra copies (≥ 3 copies). These cut-off values were applied equally in BCL2, BCL6, and MYC genes.

Statistical analysis

Bivariate analysis was carried out through cross-tabulation analysis using Chi-square test and Fisher's exact test to analyze relevance of clinicopathologic or cytogenetic features. Five-year overall survival (OS) and 5-year progression-free survival (PFS) were analyzed by Kaplan–Meier method with log rank test and life table method with Wilcoxon rank test. OS was calculated from the date of diagnosis to the date of death or the last follow-up visit. PFS was calculated from the date of starting treatment to the date when disease progression was recognized to the date of death or the last follow-up visit. Univariate Cox proportional hazard model was used to identify significant predictors of clinical outcome. All analyses were done using the Statistical Package for the Social Sciences (SPSS) 18.0.0. Statistical significance was set at the level of $p < 0.05$.

Results

Annual frequency and proportion of follicular lymphoma

A total of lymphoma cases between 1991 and 2017 was 113,851 (2.10 % of total inpatients), and the number of FL cases was 3,166 (0.06 % of total inpatients and 2.78 % of all lymphomas). Annual frequency of FL (patients with FL/total inpatients) has increased from 0.01 % in 1991 to 0.04 % in 2017 (Figure 1A). Annual proportion of FL to all lymphomas also has increased from 2.15% (120/5579 case) in 2007 to 3.75 % (319/8337 cases) in 2017 (Figure 1B).

Clinicopathological characteristics of follicular lymphoma

Median age was 51.9 years (range 15-68 years) with male to female ratio of 1.21:1. Extranodal involvement was present in 157 cases (52.9%): gastrointestinal tract, 60.9%; bone marrow, 33.8%; soft tissue, 25.2%.

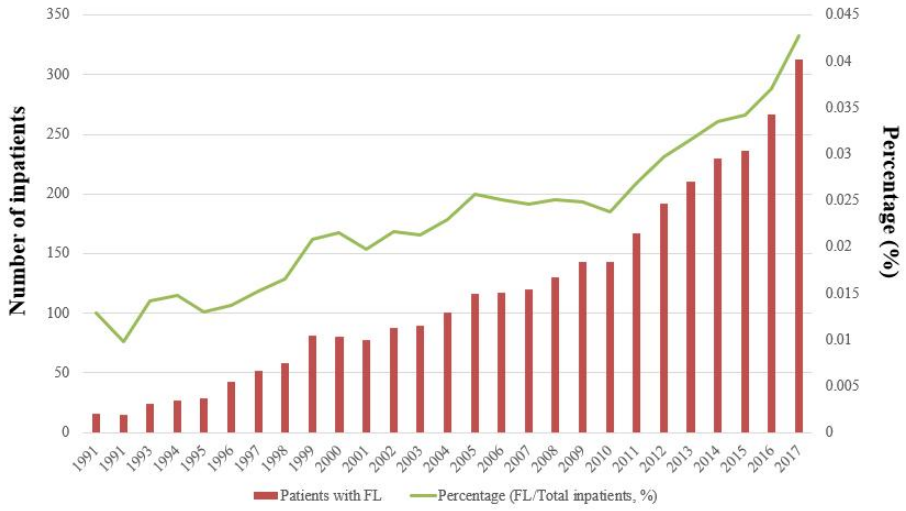

Figure 1A. Annual proportion of patients with FL to total inpatients between 1991 and 2017. The incidence has been increased from 0.01% to 0.04% between 1991 and 2017.

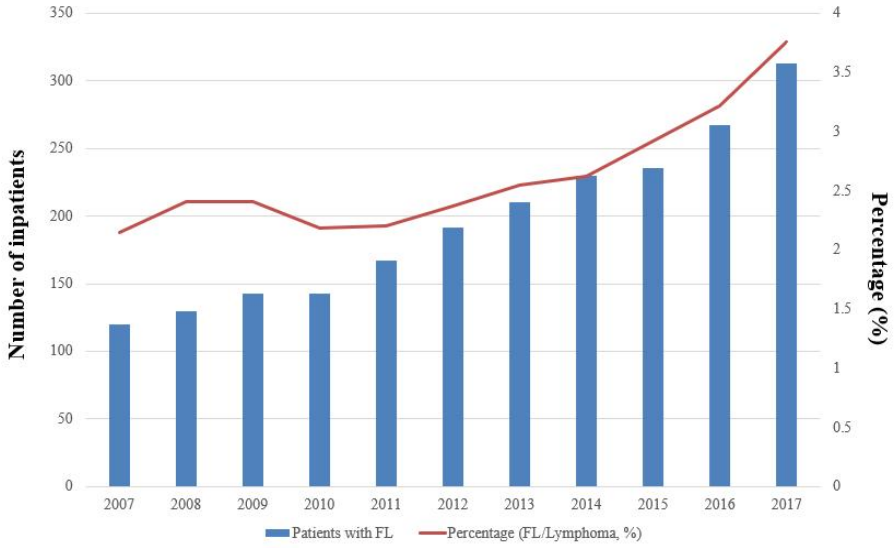

Figure 1B. Annual proportion of FL cases to all lymphoid malignancies between 2007 and 2017. The proportion has been increased from 2.15% (120 /5579 case) in 2007 to 3.75 % (319 /8337 cases) in 2017.

Majority of the cases had high stage of Ann Arbor stage (stage I-II, 39.9 %; stage III-IV, 60.1 %), and low risk group of FLIPI (low risk, 45.3%; intermediate risk, 28.3%; high risk, 26.4%). Presence of DLBCL transformation was seen in 7.2% of cases (Table 1). Chemotherapy was adopted as initial treatment for majority of patients (63.7%) (R-CHOP, 25.5 %; or R-CVP, 21.7%). Watch-and wait approach was applied in 20.0% of patients (Table 2).

Histologic grade showed predominance of low grade (FL 1/2, 64.1%; FL 3A, 24.2 %; FL 3B, 11.1 %) (Table 3). By bivariate analysis of histologic grade and immunoprofiles, FL 3B showed less frequent expression on BCL2 (P=0.488), BCL6 (P<0.05), and CD10 (P<0.001) than FL 1-2 or FL 3A (Table 3). Histologic growth pattern of FL showed significant associations with the grade (P<0.001) (Table 4).

Table 1. Baseline patients' characteristics (n=296)

Parameters	**Frequency N (%)**
Age, median (range)	51.9 years (15-68)
> 60	79 (26.7)
< 18	3 (1.01)
Sex	
Male	162 (54.72)
Female	134 (45.27)
Male to female ratio	1.21:1
B symptom	
Present	27 (9.2)
Not present	269 (90.9)
Ann Arbor stage	

Stage Ⅰ or Ⅱ	118 (39.9)
Stage Ⅲ or Ⅳ	178 (60.1)
Extra-nodal involvement	157 (52.9)
Gastrointestinal involvement	96 (60.9)
Bone marrow involvement	53 (33.8)
Soft tissue	40 (25.2)
DLBCL transformation	21 (7.2)
FLIPI* (points)	
Low risk (0-1)	134 (45.3)
Intermediate risk (2)	84 (28.3)
High risk (3-5)	78 (26.4)

* FLIPI, Follicular Lymphoma International Prognostic Index

Table 2. First-line treatment characteristics (n=296)

Treatment	**Frequency N (%)**
Watch-and wait	59 (20.0)
Chemotherapy	187 (63.4)
R-CHOP	75 (25.5)
R-CVP	64 (21.7)
Other	44 (16.2)
Radiation monotherapy	2 (0.7)
Operation	5 (1.7)

By survival analysis, the median follow-up times was 49 months (0-298 months). Five-year OS and PFS showed significant increase in a period of 2011-2017 since the introduction of rituximab. Five-year OS: 1991-2000, 53%; 2001-2010, 87% and 2011-2017, 96% (P<0.001). Fiver-year PFS: 1991-2000, 53%; 2001-2010, 75% and 2011-2017, 81% (P<0.05) (Figure 2).

Cytogenetic characteristics by FISH analysis

Evaluation of translocation and extra copies in BCL2, BCL6, and MYC genes were performed in 129 cases. The following samples which showed poor qualities to interpret translocation in FISH results were excluded: BCL2, 27 cases (20.9%); BCL6, 26 cases (20.2%); MYC, 29 cases (22.5%). Sixty-five cases (63.7%) out of 102 cases had BCL2 translocation. Fifteen cases (14.6%) out of 103 cases had BCL6 translocation. Only two cases (2.0%) out of 100 cases showed MYC translocation.

Table 3. Distribution of grade and immunostaining results of FL (n=296)

Parameters	**Frequency N (%)**	***P* value**
Histologic grade		
Grade 1-2	191 (64.1)	
Grade 3	105 (35.6)	
Grade 3A	72 (24.2)	
Grade 3B	33 (11.1)	
BCL-2 expression	232 (78.2)	
Grade 1-2	153 (90.5)	
Grade 3A	49 (86.0)	0.488
Grade 3B	21 (84.0)	
BCL-6 expression	244 (83.3)	
Grade 1-2	162 (87.1)	
Grade 3A	54 (79.4)	<0.05
Grade 3B	19 (67.9)	
CD10 expression	213 (72.2)	

Grade 1-2	154 (82.4)	
Grade 3A	45 (65.2)	<0.001
Grade 3B	10 (35.7)	

Table 4. Distribution of growth pattern and grade of FL (*P*<0.001) (n=296)

Grade of FL	Pattern*		
	Follicular	Follicular and diffuse	Diffuse
Grade 1-2	171 (92.4%)	10 (5.4%)	4 (2.2%)
Grade 3A	57 (82.6%)	9 (13.0%)	3 (4.3%)
Grade 3B	18 (54.5%)	7 (21.2%)	8 (24.2%)

*Follicular, >75% of follicular growth; Follicular and diffuse, 25-75% of follicular growth; Diffuse <25% of follicular growth

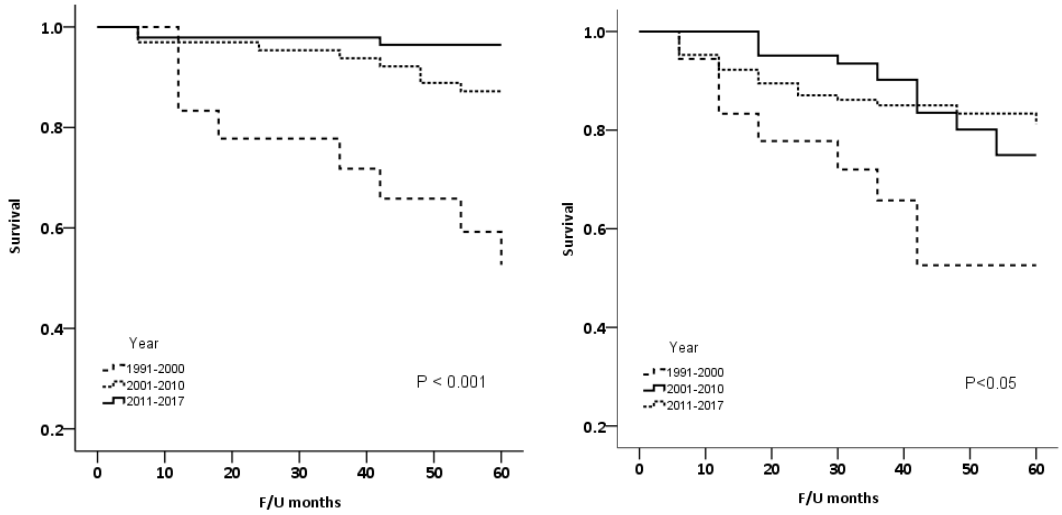

Figure 2. Fiver-year OS (left) and PFS (right) between 1991-2000, 2001-2010 and 2011-2017. The survival rate has been remarkably increased, in recent years (OS:

1991-2000, 53%; 2001-2010, 87% and 2011-2017, 96%, P<0.001; PFS: 1991-2000, 53%; 2001-2010, 75% and 2011-2017, 81%, P<0.05).

In analyses of extra copies (≥ 3 copies), 38 cases (29.5%) in BCL2, 35 cases (27.1%) in BCL6, and 30 cases (23.3%) in MYC were excluded due to poor qualities of the samples to evaluate copy number status. Based on cut-off value of 5%, 30 cases (33%) out of 91 cases in BCL2, 35 cases (37.2%) out of 94 cases in BCL6, and 15 cases (15.2%) out of 99 cases in MYC showed CNA. Figure 3 shows representative images of translocation and CNA in BCL2, BCL6, and MYC genes.

BCL2 protein expression showed weak positive correlation with BCL2 translocation (r = 0.172, P = 0.042), and weakly negative correlation with BCL6 translocation (r = - 0.390, P<0.001). Otherwise, no significant difference was observed in expression of BCL6 and MYC protein (data not shown). No significant difference was observed between CNA and immunoexpression of BCL2, BCL6, or MYC (data not shown). Most of the cases with BCL2 CNA had no BCL2 translocation (80.4%, P = 0.001). Similar pattern was observed in BCL6 or MYC gene: BCL6 CNA or MYC CNA generally did not have BCL6 or MYC translocation, respectively. However, they did not show statistical significance (P = 1.000), which is resulted in a small number of cases (data not shown).

Distribution of translocation or CNA with histologic grade and clinical features were showed in table 5A and table 5B. BCL2 translocation was associated with low grade (P < 0.001), low risk of FLIPI (P = 0.216), and absence of DLBCL transformation (P < 0.001). BCL6 CNA was associated with high grade (FL 1-2, 28.6%; FL 3A, 25.7%; 3B, 45.7%, P < 0.001), high risk of FLIPI (low, 11.4%;

intermediate, 31.4%; high, 57.1%, *P* = 0.118), and presence of DLBCL transformation (absent, 79.4%; present, 20.6%, *P* = 0.035). In contrast, BCL2 CNA and BCL6 translocation did not show significant difference with clinicopathologic features. By univariate analysis, BCL6 CNA was a worse prognostic factor for OS (*P* = 0.002) (Table 6).

We divided cases with CNA into extra copy (3-4 copies) or amplification (≥ 5 copies) groups. Differences in OS were observed between extra copy and amplification groups of BCL2 or BCL6 with decreased survival rate toward amplification group (*P* = 0.416 and 0.297, respectively), but MYC had no significant difference between the two groups, due to the small number of cases (data not shown).

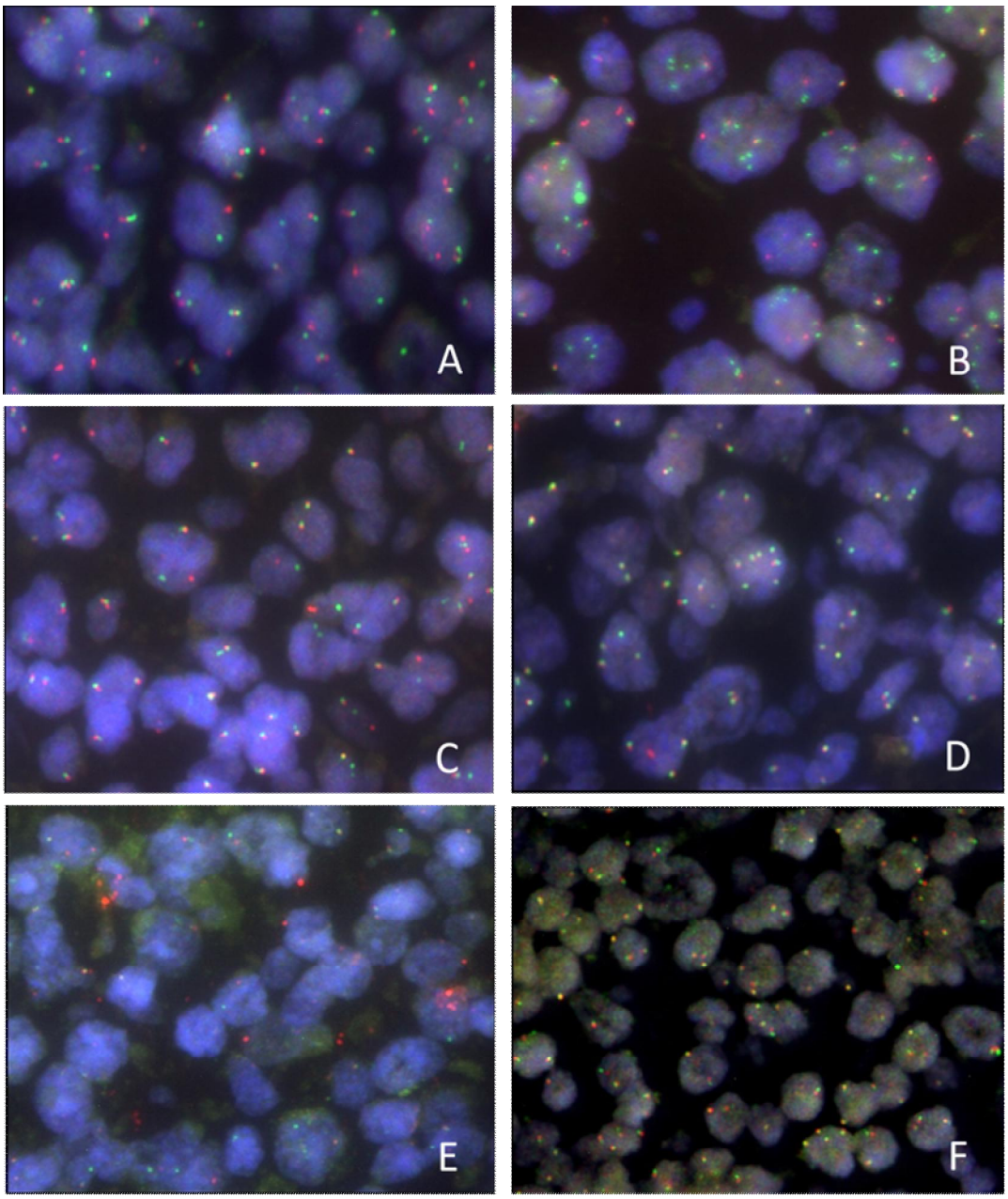

Figure 3. Representative results of translocation and copy number aberration by FISH analysis for BCL2, BCL6, and MYC. Translocation (left) and copy number aberration (right) of BCL2 (A, B), BCL6 (C, D), and MYC (E, F) are detected.

Table 5A. Translocation of BCL2, BCL6, and MYC with clinicopathologic parameters

Characteristics	BCL2, n (%)		*P* value	BCL6, n (%)		*P* value	MYC, n (%)		*P* value
	T^{+}*	T^{-}†		T^{+}	T^{-}		T^{+}	T^{-}	
Stage									
I-II	11 (16.9)	8 (21.6)	0.558	1 (7.1)	20 (22.7)	0.290	0 (.0)	18 (18.6)	1.000
III-IV	54 (83.1)	29 (78.4)		13 (92.9)	68 (77.3)		2 (100.0)	79 (81.4)	
Grade									
1-2	43 (66.2)	12 (32.4)	<0.001	6 (40.0)	49 (55.7)	0.139	1 (50.0)	52 (53.1)	0.433
3A	16 (24.6)	8 (21.6)		7 (46.7)	19 (21.6)		0 (.0)	27 (27.6)	
3B	6 (9.2)	17 (45.9)		2 (13.3)	20 (22.7)		1 (50.0)	19 (19.4)	
FLIPI									
Low	12 (18.5)	9 (24.3)	0.216	2 (14.3)	21 (23.9)	0.488	1 (50.0)	20 (20.6)	0.490
Intermediate	25 (38.4)	8 (21.6)		3 (21.4)	28 (31.8)		0 (.0)	33 (34.0)	
High	28 (43.1)	20 (54.1)		9 (64.3)	39 (44.3)		1 (50.0)	44 (45.4)	
DLBCL transformation									
Present	0 (.0)	10 (27.8)	<0.001	2 (15.4)	9 (10.2)	0.631	0 (.0)	10 (10.4)	1.000
Absent	65 (100.0)	26 (72.2)		11 (84.6)	79 (89.8)		2 (100.0)	86 (89.6)	

Table 5A. Abbreviation, * T^+, translocation; † T^-, no translocation.

Table 5B. CNA of BCL2, BCL6, and MYC with clinicopathologic parameters

Characteristics	BCL2, n (%)		*P* value	BCL6, n (%)		*P* value	MYC, n (%)		*P* value
	CNA^{+}*	CNA^{-}†		CNA^{+}	CNA^{-}		CNA^{+}	CNA^{-}	
Stage									
I-II	5 (16.7)	11 (18.0)	0.872	4 (11.4)	16 (27.6)	0.066	2 (13.3)	16 (19.3)	0.731
III-IV	25 (83.3)	50 (82.0)		31 (88.6)	42 (72.4)		13 (86.7)	67 (80.7)	
Grade									
1-2	12 (40.0)	36 (59.0)	0.204	10 (28.6)	40 (67.8)	<0.001	5 (33.3)	47 (56.0)	0.185
3A	8 (26.7)	13 (21.3)		9 (25.7)	15 (25.4)		5 (33.3)	22 (26.2)	
3B	10 (33.3)	12 (19.7)		16 (45.7)	4 (6.8)		5 (33.3)	15 (17.9)	
FLIPI									
Low	4 (13.3)	15 (24.6)	0.462	4 (11.4)	17 (29.3)	0.118	2 (13.3)	19 (22.9)	0.619
Intermediate	10 (33.3)	18 (29.5)		11 (31.4)	17 (29.3)		4 (26.7)	28 (33.7)	
High	16 (53.3)	28 (45.9)		20 (57.1)	24 (41.4)		9 (60.0)	36 (43.4)	
DLBCL transformation									
Present	6 (20.0)	4 (6.7)	0.078	7 (20.6)	3 (5.2)	0.035	1 (6.7)	9 (11.0)	1.000
Absent	24 (80.0)	56 (93.3)		27 (79.4)	55 (94.8)		14 (93.3)	73 (89.0)	

Table 5B. Abbreviation: * CNA^+, copy number aberration; † CNA^-, no copy number aberration.

Table 6. Univariate analysis for overall survival in FL

Variates		Overall survival		
		HR	95% CI	*P* value
Ann arbor stage		2.173	0.931 – 5.077	0.073
FLIPI		5.577	1.435 – 21.679	0.013
Histologic grade		4.507	2.134 – 9.517	<0.001
Translocation	BCL2	0.311	0.094 – 1.028	0.055
	BCL6	2.330	0.713 – 7.614	0.162
	MYC	7.782	0.950 – 63.717	0.056
CNA*	BCL2	1.213	0.376 – 3.916	0.747
	BCL6	11.954	2.576 – 55.473	0.002
	MYC	2.208	0.582 – 8.385	0.245

* CNA, copy number aberration.

When cases with extra copies and amplification were grouped into CNA group, OS differences were more distinct between cases without BCL6 CNA (BCL6 NL) and cases with BCL6 CNA (median OS: BCL6-NL vs BCL6 CNA, 46 vs 31 months, $P < 0.001$) (Figure 4A). MYC CNA also showed poor OS (median OS: MYC-NL vs MYC CNA, 40 vs 33 months, $P = 0.231$), but BCL2 CNA showed no significant difference (median OS: BCL2-NL vs BCL2 CNA, 37 vs 39 months, $P = 0.746$). BCL6 CNA, and MYC CNA showed worse PFS than no CNA groups (median PFS: BCL6 NL vs BCL6 CNA, 36.0 vs 12.0 months, $P = 0.038$; MYC-NL vs MYC CNA, 27.0 vs 11.0 months, $P = 0.038$, respectively). BCL2 CNA showed no significant difference in PFS (median PFS: BCL2-NL vs BCL2 CNA, 17 vs 24 months, $P = 0.726$) (Figure 4B).

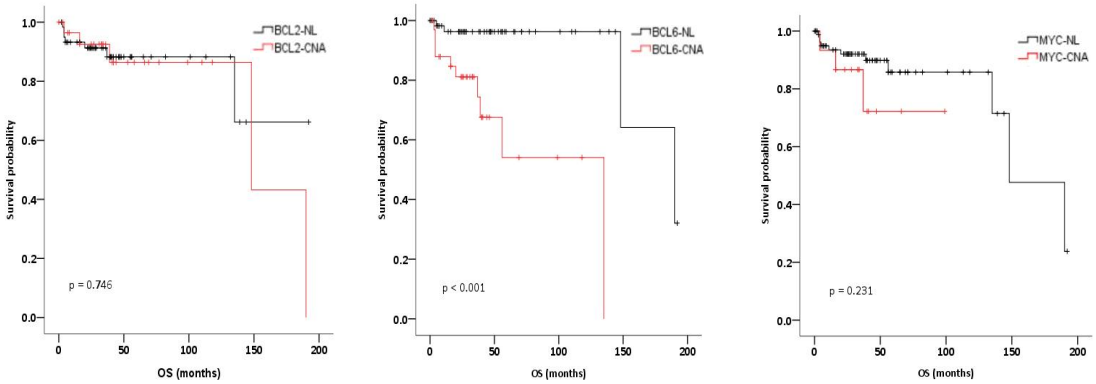

Figure 4A. Overall survival of cases grouped into copy number aberration and no copy number aberration of BCL2, BCL6, and MYC. NL, no copy number; CNA, copy number aberration.

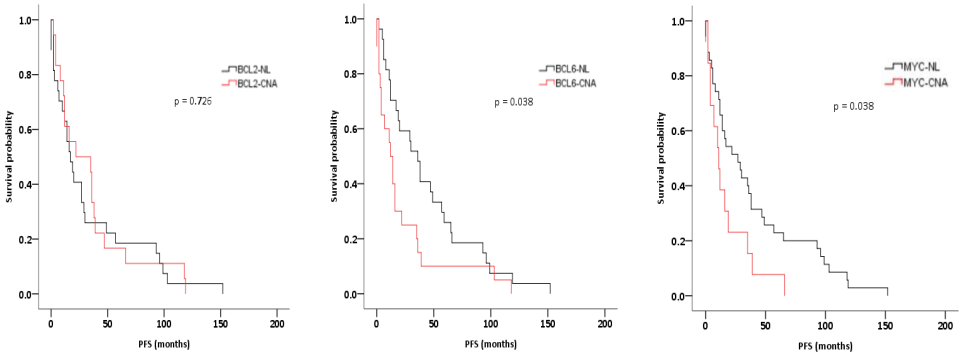

Figure 4B. Progression-free survival of cases grouped into copy number aberration and no copy number aberration of BCL2, BCL6, and MYC. NL, no copy number aberration; CNA, copy number aberration.

Discussion

In this study, we performed a systematic investigation of the incidences, overall clinicopathologic and cytogenetic features of FL in Korea population. Our study showed similar results to prior studies in histologic and cytogenetic features of FL [10, 11, 14, 18-20], and verified the association of BCL6 CNA with clinicopathologic prognosis.

FL, although it is a disease entity, shows different immunophenotypes by histologic grade. In our study, higher grade of FL showed less expression of BCL2, BCL6 and CD10 in keeping with previous studies, which described different biologic behavior in FL 3 [21-24]. However, significant association between histologic grade and clinical outcome is uncertain, especially in FL 3A.

It is questionable that FL 3A is clinically different group from FL 1-2 or FL 3B. Intra- or interobserver variability in grading of FL, especially FL 3A, also has been discussed in previous studies [25, 26]. Other prior studies revealed that FL 3A showed no significant difference with FL 1-2 or FL3B in clinical prognosis or therapeutic response [26-30]. These results may be attributed to introduction of rituximab, which contributes to survival improvement in grade of FL 3A.

By FISH analysis study, our data showed similar results in distribution of BCL2 translocation to prior studies: lower frequency of BCL2 translocation in high grade and high risk-group of FLIPI. [8, 10, 18, 20]. In contrast, clinicopathologic significance of BCL6 translocation remains uncertain. In our data, cases with BCL6 translocation were preferentially allocated in high risk group of FLIPI, however, by univariate analysis, BCL6 translocation was not significant prognositc factor. In previous studies, FL with BCL6 translocation has been frequently found in high grade or high risk group of FLIPI [20], and showed higher risk of transformation into aggressive lymphoma than FLs without BCL6

translocation [19]. However, another study described that BCL6 translocation is not associated with histologic grade [14].

A few previous studies have examined the significance of CNA of FL disease. Prior report showed copy number gain of BCL6 was associated higher histologic grade and higher expression of BCL2 and MUM1 immunostainings [14]. Another previous study showed frequent copy number gain of 3q27.3-q28 in transformed FL [31]. However, these a few studies did not show any relevance between BCL6 CNA and clinical prognosis. Our study showed worse prognosis in FL with BCL6 CNA.

For the cut-off value of CNA, we referred to the value of previous study, 5%, for reasonable applicability [14]. In current study, additional analysis was performed to find another cut-off value using control samples which were reactive tonsil or reactive lymph nodes. Using mean of normal control ± 3SD, the cut-off value were 1.8% in BCL2, 1.6% in BCL6, and 1.5% in MYC. Results of FISH analysis based on these cut-off value were similar to those with 5% cut-off value: By univariate analysis, BCL6 CNA showed worse prognosis in OS and PFS (P < 0.001 in OS and P = 0.06 in PFS, data not shown), contrary to BCL2 CNA and MYC CNA (data not shown).

This study has some limitations on cases which are analyzed by FISH. Some of the patients (17 specimens, 17 patients) which were used for FISH analysis, were not initial diagnostic biopsy specimens. The 17 patients were initially diagnosed at the outside institution, and then referred to our hospital. Even with the limitation, our study showed recent increase in incidence, clinicopathologic and cytogenetic characteristics of FL in Korea, which only a few studies have described. Of the cytogenetic features, FL with BCL6 CNA was significantly associated with poor survival outcome. This is the first report

to evaluate prognostic significance in clinicopathologic and cytogenetic features of FL in Korea population.

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국문요약

연구배경 및 목적

소포성 림프종은 비호지킨 림프종에서 미만성거대 B 세포 림프종 다음으로 흔한 종양이다. 동양에서 소포성 림프종의 발생률이 과거에는 매우 드문 질환으로 알려져 있었으나, 그 발생률이 최근 점차 증가하고 있다. 이렇게 증가하는 추세속에서, 한국에서의 소포성 림프종에 대한 연구는 많이 부족한 상황이다.

연구재료와 연구방법

소포성 림프종 환자의 임상적 및 병리학적 특징을 분석하기 위한 후향적 연구 대상자는, 서울아산병원에서 1991-2017 년에 소포성 림프종으로 진단받은 환자 296 명을 대상으로 하였다. 추가적으로 형광동소혼성화 (Fluorescence In Situ Hybridization, FISH) 분석을 통하여 소포성 림프종 환자의 세포 유전학적 특징을 보기 위한 연구 대상자는, 2013 – 2017 년의 진단 조직 검체를 사용하였다. 이에 해당되는 환자는 총 129 명으로 FISH 분석을 통해 전좌 (translocation), 혹은 복제 개수 증가 (copy number aberration, CNA) 여부를 평가하였다. 이상의 분석된 소포성 림프종 환자의 임상적, 병리학적, 및 세포유전학적 특징을 바탕으로 환자의 예후와의 관련성을 평가하였다.

연구결과

서울아산병원에서 연도별 전체 내원 환자 수 대비 소포성 림프종 환자의 분율은 꾸준히 증가하였으며, 1991 년 0.01%, 2017 년 0.04% 로 약 4 배 가까이 증가하였다. 주요 임상학적 특징 결과로서, 환자의 대부분은 (45.3%) 소포성 림프종의 림프종 국제 전조 지수 (Follicular Lymphoma International Prognostic Index, FLIPI)에서 낮은 위험 그룹에 속하였으며 7.2% 환자에서 미만성 거대 B 림프종으로 진행하였다. 환자의 대부분 (63.7%)은 초기 치료로 항암치료를 받았다 (R-CHOP, 25.5, R-CVP, 21.7%). 병리학적 특징 분석을 통한 주요 결과로는, 소포성 림프종 환자의 대부분은 (64.4%) 낮은 등급을 보였으며, 등급이 높을수록 BCL6 또는 CD10 발현율이 감소하였으며 통계적으로 유의미하였다. 소포성 림프종 세포의 등급이 높을수록, 혹은 증식하는 양상이 미만성 형태를 보일수록 종양 세포의 Ki-67 양성 분율은 증가하였고 통계적으로 유의미하였다. 높은 위험 그룹에 속하는 환자, 또는 조직학적 등급이 높은 환자 모두에게서 낮은 전체 셍존율과 무진행 생존율을 보였고 모두 통계적 유의성을 보였다.

FISH 분석결과에서는, 조직학적 등급이 높은 소포성 림프종은 BCL2 translocation 을 보이는 빈도가 적었으며 통계적으로 유의미한 결과였다. 전체 생존율과 무진행 생존율과의 다변량 분석에서, BCL6 CNA 는 독립적인 예후 인자 로서의 결과를 보여주었다 (HR, 11.884; 95% CI, 1.170 – 120.756, P = 0.036).

결론

본 연구는 소포성 림프종 환자의 최근 증가 추세와 함께, 환자의 전반적인 임상, 병리학적 및 세포유전학적 특징을 보여준다. 분석된 세포유전학적 특징에서, BCL6 CNA 를 보이는 소포성 림프종은 나쁜 예후를 보여준다. 본 연구는 한국인을 대상으로 한 임상, 병리학적 및 세포유전학적 특징을 분석하고 그에 대한 예후와의 관련성을 분석한 첫 번째 연구이다.