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Original Research Article

Prognostic impact of BCL2, BCL6 and MYC status in de novo diffuse large B-cell lymphoma: a regional study of 43 patients

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ABSTRACT

Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma with marked biologic heterogeneity. We aimed to evaluate the status of MYC, BCL2, BCL6 in patients with DLBCL.
Methods: Herein, we have investigated the prognostic relevance of MYC, BCL2 and BCL6 from 43 de novo DLBCL patients.
Results: In this study, protein overexpression of BCL2 and BCL6 was encountered in 46.5% (n=20) and 27.9% (n=12) of the tumors, respectively. Rearrangements in MYC, BCL6, and BCL2 were detected in 9.3% (n=4), 25.6% (n=11), and 4.7% (n=2) of the cases, respectively. Any statistically significant difference could not be found between Bcl-2, Bcl-6 expression, C-MYC rearrangement and the survival.
Conclusions: We concluded that C-MYC and BCL2 may contribute to aggressive transformation, so more mechanism-based therapy should be explored. A larger study is warranted to better understand the immunophenotypic and molecular features of DLBCL and their respective impact on patient survival.

Keywords: Diffuse large B-cell lymphoma, Fluorescence in situ hybridization, Immunohistochemistry, Prognosis, MYC, BCL6, BCL2,

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the fifth most frequent cancer worldwide, in which diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype in adults.[1,2] DLBCL comprises a heterogeneous group with different clinical, morphological, immunological, cytogenetic characteristics, treatment responses, and prognosis.[3] Currently, the prognosis of patients with DLBCL is estimated using the clinical parameters of the International Prognostic Index (IPI).[4]

However, these clinical parameters reflect a mixture of underlying biologic or genetic differences. Numerous studies have examined the prognostic factors for predicting survival and determining optimal therapeutic strategies in DLBCL.[1,5]

Cytogenetic and molecular cytogenetic in DLBCL showed that tumor cells carry nonrandom chromosomal aberrations, most frequently chromosomal translocations, deletions, or amplifications, as well as gene alterations and somatic hyper mutations. DNA probes are used to identify specific genetic abnormalities that provide insight into the pathogenesis of this complex disease and

to define distinct subgroups with variable prognoses. The most common chromosomal rearrangements in DLBCL are those involving chromosomal gene loci 3q27/BCL6, 8q24/MYC, and 18q21/BCL2.[2,6,7]

The BCL6 gene has been identified from the chromosomal translocation breakpoint in B cell lymphomas, and its products are expressed highly in germinal center (GC) B cells. Several studies showed that the Bcl6 is essential for the differentiation of GC B cells. BCL2 gene is also an oncogene that functions as a dominant regulator of apoptotic cell death and it promotes hemapoetic cell survival. MYC oncogene is a transcription factor which play a critical role in cell proliferation, growth, metabolism, differentiation, apoptosis, and immune response.[8-10] The nature of the C-MYC aberrations included gene translocation, gene amplification, and C-MYC mRNA or C-MYC protein overexpression. C-MYC gene translocation is a disease-initiating event and hallmark of Burkitt lymphoma (BL). It can be observed in 5-17% of de novo DLBCL and correlates with a poorer outcome.[2,10-12] Despite the advances achieved in assessing prognostic significance of C-MYC in DLBCL, recent studies have implied the prognostic value of C-MYC is complicated by other factors.[13] For example, C-MYC gene translocation was frequently found in DLBCL with concurrent translocations of BCL2 and/or BCL6, referred to as "double-hit" or "triple-hit" lymphomas, and indicated a dismal prognosis.[14,15] Although some studies have shown that the presence of C-MYC aberrations was significantly associated with shorter survival in DLBCL , other studies failed to show such an association between C-MYC and worse prognosis.[11,16-21] Therefore, the role of C-MYC as independent prognostic factors needs to be further addressed in well-designed clinical trials.[1]

In this study, the frequency of MYC, BCL2, and BCL6 rearrangements was investigated in DLBCLs using fluorescence in situ hybridization (FISH) analysis. In addition, the clinicopathological features and prognostic implications of these gene aberrations in DLBCLs treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

METHODS

Tumor biopsy or surgical specimens and clinical data were obtained before treatment from 43 patients with newly diagnosed DLBCL at Department of pathology, Izmir Tepecik Research and Training Hospital between January 2009 and December 2016. Gender of the patients, their ages at the time of diagnosis, disease stages, R-IPI scores, LDH levels, presence of B symptom, and bone marrow involvement (if any) in addition to their primary site of tumor were recorded. Besides, treatment plans of the patients, and whether rituximab was included in their treatment plans, their responses to treatment, and follow-up periods were also noted. Patients in the study were divided into 2 prognostic groups according to IPI scores as low risk (0-2), and high risk (3-5). This study was approved by Institutional Ethics Committee of Tepecik Education and Research Hospital, Turkey.

Immunohistochemistry

For immunohistochemistry (IHC), hematoxylin and eosin (HE) staining was used to select appropriate diagnostic paraffin blocks and to identify viable tumor areas. IHC was performed by the streptavidin-biotin peroxidase method (Invitrogen, Camarillo, 85-9043, USA). Serial 5µm sections were obtained and placed on slides which were baked overnight at 60^0C, dewaxed in xylene, and hydrated with distilled water through decreasing concentrations of alcohol. All slides were treated with heat-induced epitope-retrieval procedure in a microwave. In this procedure slides were left for 20minutes in 10mM/L citrate buffer at pH 6.0, cooled at room temperature for 20minutes, and then blocked to retrieve endogenous peroxidase and biotin. BCL2 (monoclonal Mouse antihuman BCL2 oncoprotein, clone 124, Dako), and BCL6 (monoclonal Mouse antihuman BCL6 protein, clone PG-B6p, Dako) were used for primary antibodies.

Fluorescence in Situ Hybridization (FISH) analysis

Interphase FISH analyses were performed on 4µm tissue sections using dual-color break apart probes for *MYC*/8q24 (Vysis LSI *MYC* Dual Color Break-Apart Rearrangement Probe, DAKO), *BCL2*/18q21 (Vysis LSI *BCL2* Dual Color Break-Apart Rearrangement Probe, DAKO), and *BCL6*/3q27 (Vysis LSI *BCL6* Dual Color Break-Apart Rearrangement Probe, DAKO) rearrangements. The slides were analyzed using an Olympus BX61 fluorescence microscope (Olympus, Tokyo, Japan). A total of 100 interphase nuclei were analyzed for each probe. Fifty to 100 nuclei were scored per case, and a case was considered positive for the rearrangement if 10% or more nuclei exhibited a break-apart signal.

Statistical analysis

Overall survival (OS) was calculated from the diagnosis until death (all-cause or event- related) or the last contact. Survival analysis was performed using Kaplan-Meier method and compared by the log-rank test. All statistical analyses were performed using SPSS IBM Statistics 20 (IBM Corporation, Chicago, USA). A P value of <0.05 was considered to be statistically significant.

RESULTS

Among 43 cases, 24 (55.8%) were male, and 19 (44.2%) were female. The age at diagnosis ranged from 23 to 86 years (median age, 62.5 years). Serum lactate dehydrogenase (LDH) levels were normal in 8 (18.6%) or elevated in 35 (81.4%) patients. When clinical symptoms of the patients were evaluated, B symptoms were present

in 25 (58.1%), and absent in 18 (41.9%) patients, respectively. The disease demonstrated nodal in 17 (39.5%), and extranodal location in 26 (60.5%) cases. Gastrointestinal system was the mostly involved extranodal region. Bone marrow involvement was present in 5 (11.6%), and absent in 38 (88.4%) cases. Demographic and clinical characteristics of the patients are shown in (Table 1).

Table 1: Clinicopathological characteristics of patients.

Characteristics of patients	DLBCL, n (%)	Overall survival/ p
Age, n (%)	62.5±15.7	
<60	20 (46.5)	0.006
≥60	23 (54.5)	
Gender, n (%)		
Male	24 (55.8)	0.360
Female	19 (44.2)	
Presentation, n (%)		
Nodal	17 (39.5)	
Extra nodal	26 (60.59	0.299
Stage, n (%)		
I- II	21 (48.8)	
III- IV	22 (51.2)	0.144
Bone marrow involvement		
Present	5 (11.6)	
Absent	38 (88.4)	0.624
Myc rearranged	4 (9.3)	0.451
Bcl6 rearranged	11 (25.6)	0.026
Bcl6 expression	12 (27.9)	0.485
Bcl2 rearranged	2 (4.7)	0.377
Bcl2 expression	20 (46.5)	0.252
Higher LDH levels	35 (81.4)	0.330
Survive (alive/ exitus)	16 (37.2)/ 27 (62.8)	-

Table 2: Clinicopathological characteristics of patients with MYC, BCL2, BCL6 rearrangements in DLBCL.

Characteristics of patients	Myc arranged	p	Bcl2 arranged	p	Bcl6 arranged	p
Patients, n (%)	4 (9.3)	-	2 (4.7)	-	11 (25.6)	-
Age, mean	50.2±8.0.9	0.061	82.2±4.2	0.083	66.0±12.9	0.573
Gender, n (%)	M= 3 (75)/ F=1(25)	0.398	F=2 (100)	0.079	M=6 (54.5), F=5 (45.6)	0.597
Presentation, n (%)	Extra nodal 4 (100)	0.121	Extra nodal 2 (100)	0.211	Extra nodal 7 (63.6)	0.548
Stage, n (%)	Advanced, 4 (100)	0.059	Advanced, 0 (0)	0.482	Advanced, 5 (45.5)	0.464
Bone marrow involvement	1 (25)	0.402	1 (50)	0.684	11 (100)	0.209
Myc rearranged	-	-	0	0.741	0	0.291
Bcl2 rearranged	0	0.741	-	-	3 (27.3)	0.184
Bcl2 expression	0	0.079	2 (100)	0.221	6 (54.5)	0.393
Bcl6 rearranged	0	0.291	2 (100)	0.184	-	-
Bcl6 expression	1(25)	0.773	2 (100)	0.077	4 (36.4)	0.360
Survival (alive/ exitus)	Exitus= 2 (50)	0.479	Exitus=2 (100)	0.237	Exitus= 10 (90.9)	0.026

Protein overexpression of BCL2 and BCL6 was encountered in 46.5 % (n=20) and 27.9 % (n=12) of the tumors, respectively. The results of BCL6 expression, and rearrangement rates were close to each other (25-27%). Contrary to BCL6, BCL2 protein expression, and rearrangement rates were very different. They were 46.5,

and 4.7%, respectively. Interestingly, all patients with BCL6 protein expression were female and there was a statistically significance between gender and BCL6 expression (p<0.01).

FISH analysis was successfully performed in 42 cases. In one patient any signal could not be elicited.

MYC rearrangements were observed in 4 (9.3%) of 42 DLBCL patients. There was no association among other clinicopathological features including age, gender (p=0.398), stage, and nodal/extranodal disease (p=0.121) and mean survival rates (p=0.479). The correlations of the previously well- known prognostic factors with C-MYC aberrations are summarized in Table 2.

BCL2 rearrangements were observed in 2 (4.6%) of 42 DLBCL patients. All of them were extranodal lymphoma, and in one patient any signal was not obtained. There was no association with other clinical features including age, gender (p=0.079), stage, CMYC (p=0.741), BCL6 rearrangements (p=0.184), mean survival (p=0.237).

BCL6 rearrangements were observed in 11 (25.6 %) of 43 DLBCL patients. All of them were cases with extranodal lymphoma. Fisher's exact test revealed a negative correlation between survival and BCL6 rearrangement (p=0.026).

The correlations of the previously well-known prognostic factors with BCL2 and BCL6 expressions are summarized in Table 3.

Table 3: Clinicopathological characteristics of patients with MYC, BCL2, BCL6 expressions in DLBCL.

Characteristics of patients	Bcl2 expression	p	Bcl6 expression	p
Patients, n (%)	20 (46.5)	-	12 (27.9)	-
Age, mean	61.1±14.7	0.083	61.8±16.4	0.904
Gender, n (%)	M=10 (50), F=10 (50)	0.079	M=1 (8.3), F=11 (91.7)	<0.01
Presentation, n (%)	Extra nodal 12 (60)	0.600	Extra nodal 11 (91.7)	0.009
Stage, n (%)	Advanced, 11 (25)	0.435	Advanced, 4 (33.3)	0.464
Bone marrow involvement	4 (20)	0.132	1 (8.3)	0.569
Myc rearranged	0	0.741	1 (8.3)	0.291
Bcl2 rearranged	2 (10)	0.221	2 (16.7)	0.184
Bcl2 expression	-	-	9 (75)	0.393
Bcl6 rearranged	6 (30)	0.393	4 (33.3	0.60
Bcl6 expression	9 (45)	0.077	-	-
Survival (alive/ exitus)	Exitus= 11 (55)	0.252	Exitus= 7 (58.3)	0.026

Double rearrangements

BCL2 and BCL6 rearrangements were observed in 2 out (3.09%) of 43 cases. These two cases were 79 (female), and 85 years old, respectively. Two cases had primary extranodal presentations. These patients had stage I disease (Figure 1, Figure 2).

For staging, modified Ann-Arbor classification was used. The cases were evaluated as stage I (n=13: 30.2%), II (n=8: 18.6%), III (n=13: 30.2%), and IV (n=9: 20.9%). In consideration of the previously indicated data in the literature, 21 (48.8%) stage I, and II cases and 22 (51.2%) stage III, and IV cases were classified in the low, and advanced stage categories, respectively.

Our cases were classified according to R –IPI risk scoring in low (n=25: 58.1%), and high risk (n=18; 41.9%) groups. Four patients with C- MYC rearrangement were classified in either low (n=3) or high (n=1) risk groups.

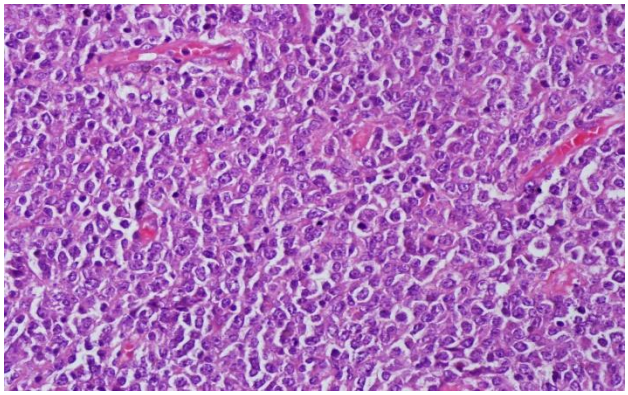

Figure 1: Diffuse large B-cell lymphoma, not otherwise specified (HE, x 400).

Survival: Sixteen patient out of 43 were living during follow-up period, while 27 of them exited. In our study overall survival rate was calculated as 37.2 %. Based on the results of the FISH method survival rates in patients with and without C-MYC rearrangement were 50 %, and

50 %, respectively. Based on log- rank analysis this difference was not statistically significant (p=0.479).

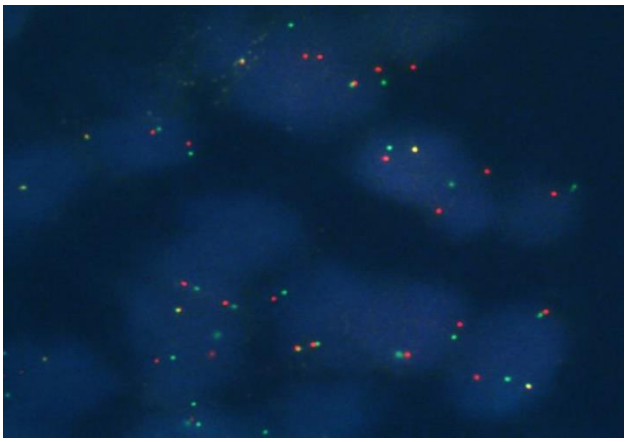

Figure 2: More than 10X nuclei exhibit break-apart signals in a case was considered positive fot the C-MYC rearrangement (DAKO FISH probe, x1000).

DISCUSSION

Cytogenetic and molecular cytogenetics in DLBCL showed that tumor cells carry nonrandom chromosomal aberrations, most frequently chromosomal translocations, deletions, or amplifications, as well as gene alterations and somatic hypermutations. DNA probes are used to identify specific genetic abnormalities that provide insight into the pathogenesis of this complex disease and to define distinct subgroups with variable prognoses. Recurrent chromosomal translocations involving the BCL6, BCL2, and/or MYC genes occur in approximately 50% of DLBCL cases.[15] These genetic changes indirectly lead to the over expression of the proteins of these genes.

It was previously reported that, the most common translocation occurred at the BCL6 locus, accounting for 20-30% of the cases. However, there are some outliers such as those from Italy, Japan, and Korea, all at around 15%.[22-24] It has been also reported that BCL6 rearrangement occurs more frequently in patients with extranodal disease. In our study, significant correlation was found between BCL6 rearrangement and BCL6 protein expression. However, we didn't determine a statistical significant correlation between BCL6 rearrangement and the extra nodal presentation (p=0.548). Most patients with BCL6 positivity had poorer survival (p=0.026).

The relative frequency of BCL2 rearrangement varied significantly among different countries, ranging from as low as 3.4% in Korea to the highest at 24.6% in Denmark. In the present study, the frequency of BCL2 rearrangement was 4.7% in DLBCL patients.[25] Moreover, we observed that BCL2 rearrangement did not correlate with BCL2 protein expression. It has been suggested that BCL2 rearrangements does not directly lead to BCL2 expression. Some alternative mechanisms may be related to up-regulation of BCL2 expression.

MYC rearrangement rate was at around 5-10% in most studies, with only an unusual high figure at 30% from China (22). The translocation rate of BCL6 in this current study (25%) was in line with the data reported in the WHO classification (up to 30%), MYC translocation rate in this study was 9.3% which was in line with the data reported in the WHO classification.[26] Our *BCL2* rearrangement rate is lower than the 20-30% rate described in the WHO classification, yet it is comparable to other East Asian countries, indicating a possible underlying ethnic difference. MYC rearrangement may coexist with BCL2 translocation in a DLBCL, so-called double-hit lymphoma; less commonly, BCL6 gene is rearranged instead of BCL2 in a double-hit lymphoma.[27] In our study MYC, plus BCL2 rearrangement was not detected.

CONCLUSION

DLBCL's have different clinical course, different response in treatment and survival because of the fact that these patients constitute a histomorphologically and genetically heterogeneous group. These genetic differences should be revealed in order to specify the effective treatments and to extend the survival. Recent studies have provided convincing evidence that a combined immunohistochemical or fluorescence in situ hybridization (FISH) score of MYC, BCL2, BCL6 proteins and MYC translocations predicted outcome in diffuse large B-cell lymphoma (DLBCL) patients treated with R-CHOP. In this study, we have investigated the prognostic relevance of MYC-, BCL2- and BCL6-rearrangements and protein expression by immunohistochemistry and FISH from 43 de novo DLBCL, patients not otherwise specified (NOS). In the literature the poor prognosis of the cases with C-MYC rearrangement, and especially those with double-hit lymphomas has been emphasized. In our study, any statistically significant correlation between the cases with C-MYC rearrangement and poor prognosis was not detected which might be related to small number of patients (4/43) with C-MYC rearrangement in our study. However larger scale studies with regular and long-term follow-ups are needed.

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REFERENCES

1. Yan LX, Liu YH, Luo DL, Zhang F, Cheng Y, Luo XL, et al. MYC expression in concert with BCL2 and BCL6 expression predicts outcome in Chinese

patients with diffuse large B-cell lymphoma, not otherwise specified. PLOS One. 2014;9(8):e104068.
2. Ye Q, Xu-Monette ZY, Tzankov A, Deng L, Wang X, Manyam GC, et al. Prognostic impact of concurrent MYC and BCL6 rearrangements and expression in de novo diffuse large B-cell lymphoma. Oncotarget. 2016;7(3):2401-16.
3. Pedersen MO, Gang AO, Poulsen TS, Knudsen H, Lauritzen AF, Nielsen SL, et al. Double-hit BCL2/MYC translocations in a consecutive cohort of patients with large B-cell lymphoma-A single centre's. Eur J Hematol. 2014;92:42-8.
4. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329:987-94.
5. Akkaya B, Salim O, Akkaya H, Ozcan M, Yucel OK, Erdem R, et al. C-MYC and BCL2 translocation frequency in diffuse large B-cell lymphomas: A study of 97 patients. Indian J Pathol Microbiol. 2016;59(1):41-6.
6. Aukema SM, Siebert R, Schuuring E, van Imhoff GW, Kluin-Nelemans HC, Boerma EJ, et al. Double-hit B-cell lymphomas. Blood. 2011;117:2319-31.
7. Sinha P, Hutter G, Kottgen E, Dietel M, Schadendorf D, Lage H. Increased expression of epidermal fatty acid binding protein, cofilin, and 14-3-3-sigma (stratifin) detected by two-dimensional gel electrophoresis, mass spectrometry and microsequencing of drug-resistant human adenocarcinoma of the pancreas. Electrophoresis. 1999;20:2952-60.
8. Xu-Monette ZY, Dabaja BS, Wang X, Tu M, Manyam GC, Tzankov A, et al. Clinical features, tumor biology, and prognosis associated with MYC rearrangement and Myc overexpression in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. Modern Pathol. 2015 Dec;28(12):1555.
9. He M, Chen K, Li S, Zhang S, Zheng J, Hu X, et al. Clinical significance of “double-hit” and “double-protein” expression in primary gastric B-cell lymphomas. J Cancer. 2016;7(10):1215.
10. Tibiletti MG, Martin V, Bernasconi B, Del Curto B, Pecciarini L, Uccella S, et al. BCL2, BCL6, MYC, MALT 1, and BCL10 rearrangements in nodal diffuse large B-cell lymphomas: a multicenter evaluation of a new set of fluorescent in situ hybridization probes and correlation with clinical outcome. Human Pathol. 2009;40(5):645-52.
11. Barrans S, Crouch S, Smith A, Turner K, Owen R, Patmore R, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol. 2010;28:3360-5.
12. Valera A, Lopez-Guillermo A, Cardesa-Salzmann T, Climent F, Gonzalez-Barca E, Mercadal S, et al. MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Haematol. 2013;98:1554-62.
13. Perry AM, Mitrovic Z, Chan WC. Biological prognostic markers in diffuse large B-cell lymphoma. Cancer Control. 2012 Jul;19(3):214-26.
14. Pfreundschuh M. Growing importance of MYC/BCL2 immunohistochemistry in diffuse large B-cell lymphomas. J Clin Oncol. 2012;30:3433-5.
15. Slack GW, Gascoyne RD. MYC and aggressive B-cell lymphomas. Adv Anat Pathol. 2011;18:219-28.
16. Akyurek N, Uner A, Benekli M, Barista I. Prognostic significance of MYC, BCL2, and BCL6 rearrangements in patients with diffuse large B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab. Cancer. 2012;118:4173-83.
17. Cuccuini W, Briere J, Mounier N, Voelker HU, Rosenwald A, Sundstrom C, et al. MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation. Blood. 2012;19(20):4619-24.
18. Peng F, Guo L, Yao WK, Zheng Y, Liu Y, Duan XM, et al. Identification of prognostic factors in patients with diffuse large B-cell lymphoma. Indian J Pathol Microbiol. 2017 Jan-Mar;60(1):87-91.
19. Horn H, Ziepert M, Becher C, Barth TF, Bernd HW, Feller AC, et al. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. Blood. 2013;121:2253-63.
20. Akasaka T, Akasaka H, Ueda C, Yonetani N, Maesako Y, et al. Molecular and clinical features of non-Burkitt's, diffuse large-cell lymphoma of B-cell type associated with the c-MYC/immunoglobulin heavy-chain fusion gene. J Clin Oncol. 2000;18:510-8.
21. Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012 Oct 1;30(28):3452.
22. Yoon SO, Jeon YK, Paik JH, Kim WY, Kim YA, Kim JE, et al. MYC translocation and an increased copy number predict poor prognosis in adult diffuse large B-cell lymphoma (DLBCL), especially in germinal centre-like B cell (GCB) type. Histopathology. 2008 Aug;53(2):205-17.
23. Kawamoto K, Miyoshi H, Yoshida N, Nakamura N, Ohshima K, Sone H, et al. MYC translocation and/or BCL 2 protein expression are associated with poor prognosis in diffuse large B-cell lymphoma. Cancer science. 2016 Jun;107(6):853-61.
24. Vitolo U, Gaidano G, Botto B, Volpe G, Audisio E, Bertini M, et al. Rearrangements of bcl-6, bcl-2, c-myc and 6q deletion in B-diffuse large-cell lymphoma: clinical relevance in 71 patients. Annals Oncology. 1998 Jan 1;9(1):55-61.
25. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, et al. CHOP chemotherapy plus rituximab compared

with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235-42.
26. Stein RA, Warnke WC, Chan ES, Jaffe JKC, Chan KC, Gatter, et al. Diffuse large B-cell lymphoma, not otherwise specified. In: Swerdlow SH, Campo E, Harris NL, et al. (Eds.), WHO classification of tumours of haematopoietic and lymphoid tissues, IARC, Lyon, France; 2008:233-237.
27. Chang ST, Chen SW, Ho CH, Kuo CC, Sakata S, Takeuchi K, et al. Immunophenotypic and genetic characteristics of diffuse large B-cell lymphoma in Taiwan. J Formosan Med Association. 2016 Nov 1;115(11):961-7.

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