Int J Clin Exp Med 2017;10(9):13564-13570
www.ijcem.com /ISSN:1940-5901/IJCEM0053528

Original Article

The phenotypes of germinal center B-cell-like (GCB) and non-GCB failed to predict the survival of patients with diffuse large B-cell lymphoma in the rituximab era

Ping Chen[1], Mao-Qing Jiang[2], Xin-Zhong Ruan[2], Nan-Li Cai[2], Xian-Wang Ye[3], Yu-Ning Pan[3], Jie Zhang[3], Xia-Ju Yang[4], Zhe-Xi Liu[4], Jun Zhang[5]

Departments of [1]Nephrology, [2]Nuclear Medicine, [3]Radiology, Ningbo First Hospital, Ningbo 315010, Zhejiang, China; Departments of [4]Pathology, [5]Nephrology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, China

Received December 15, 2016; Accepted July 6, 2017; Epub September 15, 2017; Published September 30, 2017

Abstract: The prognostic significance of the phenotypes of germinal center B-cell-like (GCB) and non-GCB in diffuse large B-cell lymphoma (DLBCL) remains uncertain. In this study, we investigated the prognostic role of the phenotypes of GCB and non-GCB and explored whether it could be improved when combined with international prognostic index (IPI) and BCL2 in patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). One hundred and six cases with de novo DLBCL were examined, and 50 patients had the GCB and 56 had the non-GCB phenotypes. The 2-year progression free survival (PFS) and overall survival (OS) were 67% and 85% in the GCB group, 55% and 82% in the non-GCB group. No significant differences of progression free survival (PFS) and overall survival (OS) were observed between these two phenotypes ($P>0.05$). When based on the same international prognostic index (IPI) risk group, the PFS and OS between the phenotypes of GCB and non-GCB still had no significant differences ($P>0.05$). Besides, patients with GCB and non-GCB showed no significant differences in PFS and OS in the BCL2 positive group and so did in the BCL2 negative group. The phenotypes of GCB and non-GCB failed to predict the survival of patients with DLBCL in the rituximab era.

Keywords: International prognostic index, diffuse large B-cell lymphoma, germinal-center phenotype, BCL2, prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL), accounting for approximately 30% to 40% of all non-Hodgkin lymphoma (NHL) cases [1], is a clinically and biologically heterogeneous [2] neoplasm. Two molecular phenotypes of DLBCL, germinal center B-cell-like (GCB) and non-GCB, which were based on the expression of CD10, bcl-6 and MUM-1 [3], had been proved to be a powerful method to predict the survival of patients with DLBCL. Patients with GCB subtype had a favorable outcome than the non-GCB [2-4]. However, this result was under controversial in various reports. Some studies [5, 6] found that the prognostic value of GCB and non-GCB was eliminated by rituximab-containing chemotherapy. Besides, other studies [7, 8] showed that the phenotypes of GCB and non-GCB had little clinical value and could not improve the prognosis of patients with DLBCL. But we found that these studies did not include the clinical characteristics of international prognostic index (IPI) in evaluating the prognostic role of GCB and non-GCB. Patients with a high IPI score had a worse outcome than the low [9]. The phenotype of GCB with a high IPI score may not have a favorable outcome than the non-GCB with a low IPI score in patients with DLBCL. Therefore, it would be better if we determined the prognostic value of GCB and non-GCB that based on the same IPI risk group.

BCL2, a mitochondrial inner-membrane protein, plays a significant role in response assessment and outcome evaluation for patients with DLBCL. Various reports demonstrated that patients with BCL2 positive had a worse outcome than the negative [10, 11]. Iqbal et al. [12] demonstrated that BCL2 was a prognostic marker

Table 1. Patients' characteristics and the difference of survival between the phenotypes of GCB and non-GCB in related clinical features

Characteristics	Patients (n, %)	GCB (n, %)	Non-GCB (n, %)	*P* value	
				PFS	OS
All patients	106 (100%)	50 (47%)	56 (53%)	0.317	0.158
Sex					
Male	65 (61%)	35 (70%)	30 (54%)	0.357	0.170
Female	41 (39%)	15 (30%)	26 (46%)	0.124	0.834
Ann arbor stage					
I-II	29 (27%)	16 (32%)	13 (23%)	0.253	0.648
III-IV	77 (73%)	34 (68%)	43 (77%)	0.496	0.336
Age (Year)					
<60	80 (75%)	44 (88%)	36 (64%)	0.159	0.483
≥60	26 (25%)	6 (12%)	20 (36%)	0.697	0.945
ECOG score					
<2	74 (70%)	39 (78%)	35 (63%)	0.114	0.287
≥2	32 (30%)	11 (22%)	21 (37%)	0.574	0.947
LDH level					
<ULN	62 (58%)	30 (60%)	32 (57%)	0.060	0.181
≥ULN	44 (42%)	20 (40%)	24 (43%)	0.956	0.989
Extranodal sites					
<2	54 (51%)	30 (60%)	24 (43%)	0.409	0.683
≥2	52 (49%)	20 (40%)	32 (57%)	0.660	0.545
IPI score					
Low (0-2)	61 (58%)	32 (64%)	29 (52%)	0.192	0.624
High (3-5)	45 (42%)	18 (36%)	27 (48%)	0.829	0.634
BCL2					
Negative	35 (33%)	17 (34%)	18 (32%)	0.711	0.705
Positive	71 (67%)	33 (66%)	38 (68%)	0.265	0.338

for patients with activated B-cell-like (ABC) DLBCL treated with CHOP-like regimens. But later, they [13] determined that the prognostic role of BCL2 had changed in DLBCL patients owing to the addition of rituximab to CHOP. The GCB DLBCL patients with BCL2 positive received less benefit from R-CHOP-like regimens. These results indicated that BCL2 was a prognostic parameter in patients with GCB or non-GCB DLBCL. However, they didn't show whether the phenotypes of GCB and non-GCB were valid prognostic markers or not when combined with BCL2 in DLBCL patients.

In this setting, we determined the prognostic value of the phenotypes of GCB and non-GCB and explored whether it could be improved when combined with IPI and BCL2 in patients with DLBCL treated with R-CHOP.

Materials and methods

Patients

We retrospectively analyzed 106 patients with newly diagnosed DLBCL. All patients were treated with rituximab combined with cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) chemotherapy between Jan 2006 to Dec 2013. Patients were excluded if the clinical information and histological features were not available. The patients' characteristics of sex, age, Eastern cooperative oncology group (ECOG) performance status, Ann arbor stage, number of extranodal sites involvements, LDH level and IPI score were summarized in **Table 1**. This study was approved by the Ethics Committee of the institution of the southern medical university, Guangzhou, China. Informed consent was waived because the nature of this retrospective study.

Immunohistochemistry

All biopsy specimens were analyzed independently by 2 pathologists (Yang XJ and Liu ZX). Fresh 4 micrometer sections were obtained from the formalin-fixed, paraffin embedded tissue. The presences of DLBCL were confirmed by the sections that stained with hematoxylin and eosin. Stainings for BCL2 (clone 124, Dako, Denmark), BCL-6 (clone P1F6, Novocastra, UK), CD10 (clone 56C6, Novocastra, UK), and MUM-1 (clone MUM1p, Dako, Denmark) were performed using antibody dilutions 1:10, 1:20, 1:20, and 1:100, respectively. According to previous study, if 30% or more of the tumor cells were stained with an antibody (BCL2, CD10, BCL-6 and MUM1), the samples were scored positive. Immunohistochemical features for CD10, BCL-6, and MUM1 were used to identify the phenotypes of GCB and non-GCB according to Hans' criteria [3].

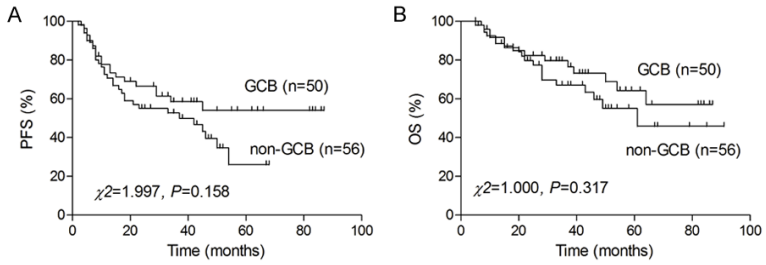

Figure 1. Progression-free survival (A) and Overall survival (B) curves according to the phenotypes of germinal center B-cell-like (GCB) and non-GCB in DLBCL patients.

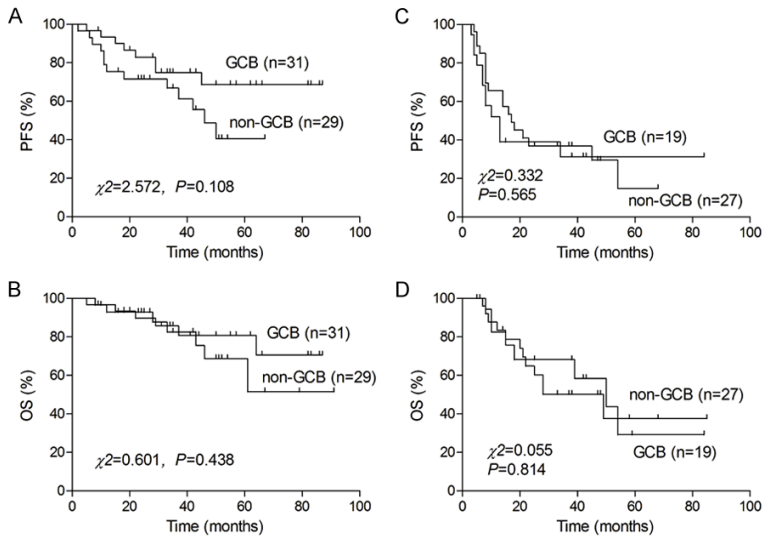

Figure 2. Outcomes according to the phenotypes of GCB and non-GCB DLBCL which based on the same IPI risk groups. (A-D) are the PFS and OS curves of patients with GCB and non-GCB DLBCL in the low (score 0-2) and high (score 3-5) risk groups of S-IPI, respectively.

Statistical analysis

Descriptive statistics of clinical characteristics were generated as proportions. The differences in the frequency of individual prognostic factors were assessed by chi-square test. End points were progression free survival (PFS; defined as time from diagnosis to progression, relapse, or death from any cause) and overall survival (OS; defined as time from diagnosis to death from any cause). The survival curves of PFS and OS were determined by Kaplan-Meier analysis. The log-rank test was used for the comparison of statistical differences between the survival curves in clinical and pathological parameters. All tests were considered significant at the two-sided 0.05 significance level. GraphPad Prism version 5.0 (GraphPad software, Inc., La Jolla, CA, USA) was used to perform statistical analysis.

Results

The patients' outcome and related clinical information

The clinical features and outcomes of 106 patients with DLBCL were summarized in **Table 1**. Patients (n=106) with DLBCL had a median age of 61 years (range, 20-82 years). The 2-year PFS and OS in the GCB group were 67% and 82%, respectively. In the non-GCB group, the 2-year PFS and OS were 55% and 82%, respectively. No significant differences of PFS and OS were observed between these two phenotypes (χ^2=1.997, P=0.158 and χ^2=1.000, P=0.317; respectively) (**Figure 1A** and **1B**). In univariate analysis, no significant differences of PFS and OS were observed between the phenotypes of GCB and non-GCB which were based on the same clinical features, such as sex (male or female), age (<60 or ≥60 years), clinic stage (stage IV), LDH level (normal or high), ECOG score (<2 or ≥2) and number of extranodal sites (<2 or ≥2) (**Table 1**).

S-IPI and the phenotypes of GCB and non-GCB for predicting the survival of patients with DLBCL

According to the IPI score, out of the total 106 patients, 21 patients (20%) were sub-classified as score 0, 39 (37%) as score 1-2, 22 (21%) as score 3 and 24 (22%) as score 4-5. We combined the patients with score 0 and score 1-2 as a low risk group, score 3 and score 4-5 as a high risk group. Obviously, significant differences were observed between the low (score 0-2) and high (score 3-5) risk groups in PFS (χ^2=16.17, P<0.001) and OS (χ^2=10.83, P=0.001). In the low risk group (score 0-2), 31

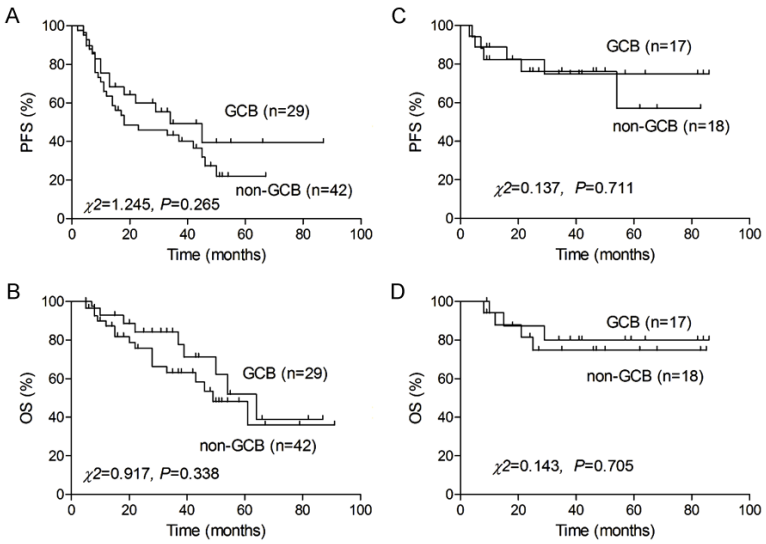

Figure 3. Outcomes according to thephenotypes of GCB and non-GCB DLBCL which based on the same BCL2 risk groups. A-D are the PFS and OS curves of patients with GCB and non-GCB DLBCL in the positive and negative groups of BCL2, respectively.

patients were sub-classified as GCB group and 29 patients as non-GCB group, and no significant differences of PFS and OS were observed between GCB and non-GCB groups (both $P>0.05$, **Figure 2A** and **2B**). Similarly, 19 patients were sub-classified as GCB group and 27 patients as non-GCB group in the high risk group (score 3-5), and no significant differences of PFS and OS were observed between these two phenotypes (both $P>0.05$, **Figure 2C** and **2D**).

BCL2 and the phenotypes of GCB and non-GCB for predicting the survival of patients with DLBCL

Various reports showed that patients with BCL2 positive revealed a poor outcome. In our results, 71 patients were BCL2 positive and 35 patients were BCL2 negative. The 2-year PFS and OS were 52% and 79% in the BCL2 positive group. And in the BCL2 negative group, the 2-year PFS and OS were 79% and 84%, respectively. Statistical analysis showed that patients with BCL2 positive indicated a poor PFS ($P<0.01$), but not in OS ($P>0.05$). In the BCL2 positive group, 29 patients were sub-classified as GCB group and 42 patients as non-GCB group, and no significant differences of PFS and OS were observed between GCB and non-GCB groups (both $P>0.05$, **Figure 3A** and **3B**). In the BCL2 negative group, 17 patients were sub-classified as GCB group and 18 patients as non-GCB group, and no significant differences of PFS and OS were observed between these two phenotypes (both $P>0.05$, **Figure 3C** and **3D**).

Discussion

Our results demonstrated that the phenotypes of germinal center B-cell-like (GCB) and non-GCB which were based on the expression of CD10, Bcl-6 and MUM1 failed to predict the survival of patients with diffuse large B-cell lymphoma in the rituximab era. The IPI showed a powerful method to predict the survival of patients with DLBCL. Patients with BCL2 positive revealed a poor PFS, but not in OS. However, even though patients based on the same IPI risk group or the same BCL2 risk group, the phenotypes of GCB and non-GCB still had no ability to differentiate the outcome of patients with DLBCL.

During the past decades, people have realized that DLBCL is not only a clinically heterogeneous, but also a molecular heterogeneity [2]. At first, DLBCL was divided into 3 subgroups termed germinal center B-cell-like (GCB), activate B-cell-like (ABC) and a type 3 by gene expression profiling [14]. Owing to the similar outcome of type 3 and ABC subtype, both of them were aggregated together as non-GCB group. The most widely used criteria to designate patients as GCB and non-GCB was Hans' algorithm [3] which were based on the expression of CD10, bcl-6, or MUM1 by immunohistochemistry. Several studies [3, 4, 15] confirmed that the phenotype of GCB in DLBCL had a significantly better survival than the non-GCB, but not in all [7, 8, 16]. Nyman et al. [6] revealed that the prognostic role of GCB and non-GCBin DLBCL patients was eliminated in the rituximab era. Ilic et al. [7] also found that no significant differences of the survival were observed between the phenotypes of GCB and non-GCB, irrespectively whether they had treated with or without rituximab. In our study, no significant difference of survival was observed between the phenotypes of GCB and non-GCB.

From the constituent elements, we found that the phenotypes of GCB and non-GCB were not associated with the clinical features, such as age, clinic stage, performance status, LDH level, and extranodal involvements. The international prognostic index (IPI) [17], owing to include these five risk factors, is the most commonly used prognostic factor in survival for patients with DLBCL in the last two decades, even though in the rituximab era [9]. Our results indicated that the IPI had a significant prognostic role to differentiate DLBCL patients into the low and high risk groups. As no significant difference of survival was observed between the phenotypes of GCB and non-GCG in DLBCL patients, we supposed it might be equitable if there were based on the same IPI risk group. However, in our study, we found that even in the same low or high risk group, there still were no significant differences between GCB and non-GCB phenotypes in PFS and OS. Besides, we also found that there were no significant differences with regard to the clinical features of sex, age, performance status, stage, extranodal sites and LDH level.

BCL2 plays an important role in outcome evaluation of patients with DLBCL. Patients with BCL2 positive had a worse outcome than the negative [10, 11]. Iqbal et al. [12] demonstrated that BCL2 was a prognostic marker for patients with ABC DLBCL treated with CHOP-like regimens. But later, they [13] determined that the prognostic role of BCL2 had changed in DLBCL patients owing to the addition of rituximab to CHOP. However, they didn't show whether the phenotypes of GCB and non-GCB were valid prognostic phenotypes or not when combined with BCL2 in DLBCL patients. In our results, patients with BCL2 positive had a worse PFS in DLBCL patients, but not in OS. The phenotypes of GCB and non-GCB still had no significant role in predicting the survival of patients with DLBCL when based on the same BCL2 risk group.

Recently, studies have indicated that the expression of CD40 is a positive prognostic factor of patients with DLBCL treated with R-CHOP [18]. Besides, other studies have showed that the expression of CD23 and CD40 may identify a favorable subgroup of DLBCL [19]. Moreover, numerous studies have demonstrated that the MYC rearrangement is associated with a poorer survival in DLBCL patients treated with R-CHOP [20, 21]. Now, more studies [22-24] have indicated that the role of MYC is forcefully influenced by BCL2. Patients with MYC and BCL2 translocation may have poor outcomes in DLBCL patients. Therefore, using only these three markers (CD10, Bcl-6 and MUM1) to designate patients as GCB and non-GCB is insufficient. The heterogeneity of DLBCL is remarkable complexity and we need to integrate all these molecular targets to seek a more effective method to improve the prognostication and to allow for the possibility of personalized therapy.

In conclusion, the phenotypes of GCB and non-GCB based on the expression of CD10, Bcl-6 and MUM1 have failed to predict the outcome of patients with DLBCL in the rituximab era. The classification of GCB and non-GCB should not be used to guide the clinical decisions for patients with DLBCL.

Disclosure of conflict of interest

None.

Address correspondence to: Jun Zhang, Department of Nephrology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, China. Tel: +86-13566624635; Fax: +86-574-87085093; E-mail: 252180843@qq.com

References

[1] Sabattini E, Bacci F, Sagramoso C and Pileri SA. WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview. Pathologica 2010; 102: 83-87.

[2] Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J Jr, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO and Staudt LM. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000; 403: 503-511.

[3] Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Muller-Hermelink HK, Campo E, Braziel RM, Jaffe ES, Pan Z, Farinha P, Smith LM, Falini B, Banham AH, Rosenwald A, Staudt LM, Connors JM, Armitage JO and Chan WC. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004; 103: 275-282.

[4] Berglund M, Thunberg U, Amini RM, Book M, Roos G, Erlanson M, Linderoth J, Dictor M, Jerkeman M, Cavallin-Stahl E, Sundstrom C, Rehn-Eriksson S, Backlin C, Hagberg H, Rosenquist R and Enblad G. Evaluation of immunophenotype in diffuse large B-cell lymphoma and its impact on prognosis. Mod Pathol 2005; 18: 1113-1120.

[5] Moskowitz CH, Zelenetz AD, Kewalramani T, Hamlin P, Lessac-Chenen S, Houldsworth J, Olshen A, Chaganti R, Nimer S and Teruya-Feldstein J. Cell of origin, germinal center versus nongerminal center, determined by immunohistochemistry on tissue microarray, does not correlate with outcome in patients with relapsed and refractory DLBCL. Blood 2005; 106: 3383-3385.

[6] Nyman H, Adde M, Karjalainen-Lindsberg ML, Taskinen M, Berglund M, Amini RM, Blomqvist C, Enblad G and Leppa S. Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. Blood 2007; 109: 4930-4935.

[7] Ilic I, Mitrovic Z, Aurer I, Basic-Kinda S, Radman I, Ajdukovic R, Labar B, Dotlic S and Nola M. Lack of prognostic significance of the germinal-center phenotype in diffuse large B-cell lymphoma patients treated with CHOP-like chemotherapy with and without rituximab. Int J Hematol 2009; 90: 74-80.

[8] Veelken H, Vik Dannheim S, Schulte Moenting J, Martens UM, Finke J and Schmitt-Graeff A. Immunophenotype as prognostic factor for diffuse large B-cell lymphoma in patients undergoing clinical risk-adapted therapy. Ann Oncol 2007; 18: 931-939.

[9] Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M and Loeffler M. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol 2010; 28: 2373-2380.

[10] Choi YW, Ahn MS, Choi JH, Lee HW, Kang SY, Jeong SH, Park JS, Han JH, Kim JH and Sheen SS. High expression of Bcl-2 predicts poor outcome in diffuse large B-cell lymphoma patients with low international prognostic index receiving R-CHOP chemotherapy. Int J Hematol 2016; 103: 210-218.

[11] Cottereau AS, Lanic H, Mareschal S, Meignan M, Vera P, Tilly H, Jardin F and Becker S. Molecular profile and FDG-PET/CT total metabolic tumor volume improve risk classification at diagnosis for patients with diffuse large B-cell lymphoma. Clin Cancer Res 2016; 22: 3801-3809.

[12] Iqbal J, Neppalli VT, Wright G, Dave BJ, Horsman DE, Rosenwald A, Lynch J, Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Campo E, Ott G, Muller-Hermelink HK, Delabie J, Jaffe ES, Grogan TM, Connors JM, Vose JM, Armitage JO, Staudt LM and Chan WC. BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. J Clin Oncol 2006; 24: 961-968.

[13] Iqbal J, Meyer PN, Smith LM, Johnson NA, Vose JM, Greiner TC, Connors JM, Staudt LM, Rimsza L, Jaffe E, Rosenwald A, Ott G, Delabie J, Campo E, Braziel RM, Cook JR, Tubbs RR, Gascoyne RD, Armitage JO, Weisenburger DD and Chan WC. BCL2 predicts survival in germinal center B-cell-like diffuse large B-cell lymphoma treated with CHOP-like therapy and rituximab. Clin Cancer Res 2011; 17: 7785-7795.

[14] Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, Gascoyne RD, Muller-Hermelink HK, Smeland EB, Giltnane JM, Hurt EM, Zhao H, Averett L, Yang L, Wilson WH, Jaffe ES, Simon R, Klausner RD, Powell J, Duffey PL, Longo DL, Greiner TC, Weisenburger DD, Sanger WG, Dave BJ, Lynch JC, Vose J, Armitage JO, Montserrat E, Lopez-Guillermo A, Grogan TM, Miller TP, LeBlanc M, Ott G, Kvaloy S, Delabie J, Holte H, Krajci P, Stokke T, Staudt LM; Lymphoma/Leukemia Molecular Profiling P. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002; 346: 1937-1947.

[15] van Imhoff GW, Boerma EJ, van der Holt B, Schuuring E, Verdonck LF, Kluin-Nelemans HC and Kluin PM. Prognostic impact of germinal center-associated proteins and chromosomal breakpoints in poor-risk diffuse large B-cell lymphoma. J Clin Oncol 2006; 24: 4135-4142.

[16] Dupuis J, Gaulard P, Hemery F, Itti E, Gisselbrecht C, Rahmouni A, Copie-Bergman C, Briere J, El Gnaoui T, Gaillard I, Meignan M and Haioun C. Respective prognostic values of germinal center phenotype and early (18)fluorodeoxyglucose-positron emission tomography scanning in previously untreated patients with diffuse large B-cell lymphoma. Haematologica 2007; 92: 778-783.

[17] The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987-994.

[18] Song G, Ni H, Zou L, Wang S, Tian F, Liu H and Cho WC. Expression of CD40 is a positive prognostic factor of diffuse large B-cell lymphoma treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Onco Targets Ther 2016; 9: 3799-3805.

[19] Linderoth J, Jerkeman M, Cavallin-Stahl E, Kvaloy S, Torlakovic E; Nordic Lymphoma Group S. Immunohistochemical expression of CD23 and CD40 may identify prognostically fa-

vorable subgroups of diffuse large B-cell lymphoma: a Nordic Lymphoma Group Study. Clin Cancer Res 2003; 9: 722-728.

[20] Barrans S, Crouch S, Smith A, Turner K, Owen R, Patmore R, Roman E and Jack A. 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: 3360-3365.

[21] Savage KJ, Johnson NA, Ben-Neriah S, Connors JM, Sehn LH, Farinha P, Horsman DE and Gascoyne RD. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood 2009; 114: 3533-3537.

[22] Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, Scott DW, Tan KL, Steidl C, Sehn LH, Chan WC, Iqbal J, Meyer PN, Lenz G, Wright G, Rimsza LM, Valentino C, Brunhoeber P, Grogan TM, Braziel RM, Cook JR, Tubbs RR, Weisenburger DD, Campo E, Rosenwald A, Ott G, Delabie J, Holcroft C, Jaffe ES, Staudt LM and Gascoyne RD. 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; 30: 3452-3459.

[23] Zaman S, Gillani JA and Rasheed R. Double-hit lymphoma - a rare subset of diffuse large B cell lymphoma with poor outcome. J Coll Physicians Surg Pak 2016; 26: 865-867.

[24] Wang XJ, Jeffrey Medeiros L, Bueso-Ramos CE, Tang G, Wang S, Oki Y, Desai P, Khoury JD, Miranda RN, Tang Z, Reddy N and Li S. P53 expression correlates with poorer survival and augments the negative prognostic effect of MYC rearrangement, expression or concurrent MYC/BCL2 expression in diffuse large B-cell lymphoma. Mod Pathol 2017; 30: 194-203.