RESEARCH ARTICLE

Prognostic Values of Various Clinical Factors and Genetic Subtypes for Diffuse Large B-cell lymphoma Patients: A Retrospective Analysis of 227 Cases

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Abstract

Aim: To analyze the significance of different clinical factors for prognostic prediction in diffuse large B-cell lymphoma (DLBCL) patients. Methods: Two hundred and twenty-seven DLBCL patients were retrospectively reviewed. Patients were managed with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen or rituximab plus the CHOP (RCHOP) regimen. Results: Lactate dehydrogenase (LDH), β2-microglobulin (β2-M), B symptoms, Ann Arbor stage and genetic subtypes were statistically relevant in predicting the prognosis of the overall survival (OS). In the CHOP group, the OS in patients with germinal center B-cell-like (GCB)(76.2%) was significantly higher than that of the non-GCB group (51.9%, *P*=0.032). With RCHOP management, there was no statistical difference in OS between the GCB (88.4%) and non-GCB groups (81.9%, *P*=0.288). Conclusion: Elevated LDH and β2-M levels, positive B symptoms, Ann Arbor stage III/IV, and primary nodal lymphoma indicate an unfavorable prognosis of DLBCL patients. Patients with GCB-like DLBCL have a better prognosis than those with non-GCB when treated with the CHOP regimen. The RCHOP treatment with the addition of rituximab can improve the prognosis of patients with DLBCL.

Keywords: Diffuse large B-cell lymphoma - prognostic analysis - genetic subtypes - rituximab - overall survival

Asian Pacific J Cancer Prev, **14 (2)**, 929-934

Introduction

Diffuse large B-cell lymphoma (DLBCL) is defined by the World Health Organization (WHO) Classification as a heterogeneous entity, encompassing morphologic and genetic variants with variable clinical presentations and outcomes and it is the most common type of non-Hodgkin's lymphoma (NHL) in adults. In Western countries, DLBCL accounts for about 31% of NHL cases and the percentage in Asia is over 40% (Alizadeh et al., 2000), with primary extra nodal NHL representing 25-40% of all non-Hodgkin's cases (Krol et al., 2003).

The development of a GeneChip technique provides an opportunity to take a genome-wide approach to predict the treatment outcome of diffuse large B-cell lymphoma (DLBCL) (Alizadeh et al., 2000; Shipp et al., 2002). Using cDNA or oligonucleotide microarrays, several studies showed that DLBCL can be subdivided into prognostically significant subgroups with germinal center B-cell-like (GCB), activated B-cell-like (ABC), and type 3 subgroups based on gene expression profiles, distinguished by expressing signatures of genes related to B-cell differentiation stages (Rosenwald et al., 2002; Poulsen et al., 2005). The latter two are inclusively named non-GCB subtype. It has been demonstrated that when treated with CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) the prognosis of patients with non-GCB DLBCL had a poorer outcome than those with the GCB-like DLBCL (Lenz et al., 2008). In former decades, some features of the microarray technique, including its high cost, the need of specific sophisticated instrumentation, and highly trained personnel, limited its application for routine clinical prognostic analysis, but in recent years, the application of immunohistochemical methods in measuring genetic subtypes enables their detection as a routine clinical examination (Naz et al., 2011), making it a significant factor in predicting the prognosis in our daily clinical practice.

Lactate dehydrogenase (LDH) is an important enzyme catalyzing the reversible transformation of pyruvate to lactate. Previous studies have reported differential expression of various LDH isoforms in specific cancers. For example, LDH1 (LDH B) was found to be significantly up-regulated in lung cancer (Chen et al., 2006), while LDH5 (LDH A) was recently shown to be involved in both tumor initiation as well as its maintenance. In

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addition LDH5 or LDHA were reported to be related with colorectal cancer metastasis and prostate cancer (Karan et al., 2002; Koukourakis et al., 2006). β2-microglobulin (β2-M), a 11kDa non-glycosylated protein, exists in all nucleated cells (Cunningham et al., 1973; Güssow et al., 1987) and is involved in the regulation of the host immune response (Townsend et al., 1986; Pedersen et al., 1994), as well as a growth factor and signaling molecule in cancer cells. β2-M expression increases during progression of human prostate cancer (Gross et al., 2007), breast cancer (Teasdale et al., 1977), renal cancer (Hemmingsen and Skaarup, 1977), lung cancer (Shuster et al., 1976), colon cancer (Ward et al., 2008), and a number of liquid tumors (Yang et al., 2006).

CHOP regimen was once the classical first-line treatment for DLBCL, but the development of monoclonal antibodies has led to a distinguished improvement in the outcome of DLBCL treatments. Currently, patients with DLBCL are medicated with immunochemotherapy, usually Rituximab, plus CHOP (RCHOP) regimen. Despite the improved outcome of patients receiving this therapy, there is still a considerable number of patients who do not respond to the treatment, promoting the urgency of discovering reliable prognostic markers that may guide alternative treatment options.

To identify the subgroups of patients with poorer prognosis in the Chinese population in order to choose better chemotherapy regimens for them, we performed a retrospective study to evaluate the prognostic factors in Chinese patients with DLBCL. In this research, we examined several markers including genetic subtypes, serum LDH levels and serum β2-M levels in 227 patients with DLBCL in our hospital, in order to find a most favorable combination of factors to predict their prognosis. We also evaluated the Rituximab treatment efficacy in these patient groups.

Materials and Methods

We reviewed 248 consecutive newly diagnosed patients with DLBCL who were hospitalized in the First Affiliated Hospital of Medical School of Zhejiang University between February 2009 and April 2011. All diagnoses were confirmed by histopathological staining of hematoxylin and eosin (HE) as well as determination of the immunophenotype according to the World Health Organization Classification. Complete clinical profiles were obtained in 227 patients who finished the follow up. Clinical staging and diagnostic methods included a clinical history and physical examination, chest, abdominal and pelvic computed tomography (CT) scans, full-digital full-body color Doppler ultrasonic diagnostic analyzer, marrow aspirate and biopsy, as well as measurement of serum LDH and serum β2-M levels (Conconi et al., 2000). Patients were segregated in to GCB-like DLBCL and non-GCB DLBCL according to results of immunohistochemistry markers CD10, BCL6 and MUM1. In 227 patients, 79 cases were treated with only CHOP (median courses was 6; range, 4-8) because of economical burden and 148 cases with RCHOP (median courses was 6; range, 4-8). The median follow-up time was 19 months (range, 1 to 40 months). The research was approved by the Ethical committee of the First Affiliated Hospital of Medical School of Zhejiang University and informed consent was obtained from all participants.

This analysis is based on the data obtained during the follow-up from February 2009 to April 2012. Therapeutic outcomes were compared between different levels of individual prognostic candidates. Overall survival (OS) rate and survival curves were calculated by the Kaplan-Meier method. OS rate was calculated from the date of diagnosis to the date of death or the last follow-up. The multivariate analysis of outcome in terms of OS was performed by Cox regression, which included the variables that were significant in a univariate analysis. Two-tailed p-values of less than 0.05 were considered statistically significant. All statistical analyses were performed with the SPSS software for Windows V. 19.0.

Results

Patient characteristics

The clinical characteristics are summarized in Table 1. The patients' average age was 53.2 years old, and the patients' median age was 54 years old. There were 149

Table 1. Baseline Characteristics

Factors	Numbers (%)	OS	*P* value
Age			
>60	70(30.8)	72.90%	*P*=0.354
≤60	157(69.2)	77.70%	
Gender			
Male	128(56.4)	72.70%	*P*=0.135
Female	99(42.7)	80.80%	
LDH			
>225U/L	101(44.5)	61.40%	*P*<0.001
≤225U/L	126(55.5)	88.10%	
β2-M>2200μg/L	96(42.3)	68.80%	*P*=0.012
≤2200μg/L	136(57.7)	81.70%	
B symptoms			
With	75(33.0)	64.00%	*P*=0.002
Without	152(67.0)	82.20%	
Primary nodal lymphoma	112(49.3)	69.60%	*P*=0.033
Extra nodal involvement lymphoma	115(50.7)	82.60%	
Ann Arbor stage			
I/II	42(18.5)	95.20%	*P*=0.002
III/IV	185(81.5)	71.90%	
IPI			
0-1	73(32.1)	97.30%	——
2	51(22.5)	80.40%	
3	54(23.8)	61.10%	
4/5/13	49(21.6)	57.10%	
Genetic subtype			
GCB	66(29.1)	84.80%	*P*=0.028
non-GCB	161(70.9)	72.70%	
treatment			
CHOP	79	62.00%	*P*<0.001
RCHOP	148	83.80%	

OS, overall survival; LDH, lactate dehydrogenase; β2-M, β2-microglobulin; IPI, international prognostic index; GCB, germinal center B-cell-like; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; RCHOP, Rituximab plus CHOP

Table 2. Univariate and Multivariate Analyses of Clinical Factors for OS Rates of DLBCL Patients

Variables	OS					
	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Age>60 y	1.299	0.743-2.272	0.359	1.209	0.676-2.162	0.522
Sex, male	0.657	0.376-1.149	0.14	0.629	0.356-1.111	0.11
Ann Arbor stage III/IV	6.708	1.634-27.545	0.008	4.211	0.997-17.790	0.051
Positive B-symptoms	2.67	1.328-3.868	0.003	1.426	0.768-2.647	0.261
LDH level>ULN (225 U/L)	3.702	2.039-6.720	<0.001	2.791	1.499-5.199	0.001
β2-M>ULN (2200 μg/L)	1.964	1.147-3.362	0.014	0.978	0.509-1.880	0.947
extra nodal involvement	0.554	0.319-0.963	0.036	0.716	0.405-1.266	0.251
non-GCB subtype	2.117	1.063-4.214	0.033	2.113	1.041-4.288	0.038

OS, overall survival; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; β2-M, β2-microglobulin; GCB, germinal center B-cell-like

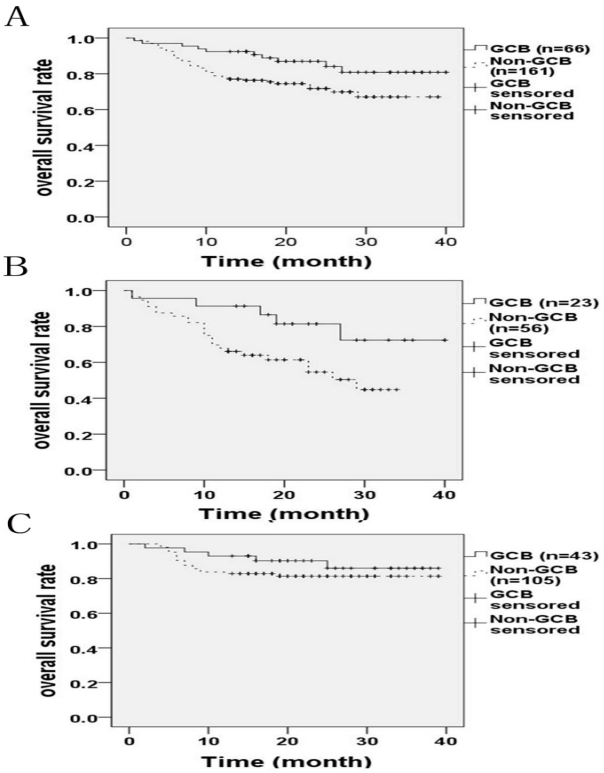

Figure 1. Patients were Divided into GCB and Non-GCB Groups According to Their Genetic Subtype, Resulting in 66 and 161 Patients in Each Group. The OS in the GCB group (84.8%) was significantly higher than that of the non-GCB group (72.7%, *P*=0.028). Figure 1B. The outcomes according to genetic subtypes for patients who received CHOP regimen showed that the OS in the GCB group (78.3%) was significantly higher than that of the non-GCB group (55.4%, *P*=0.037). Figure 1C. Outcomes according to genetic subtypes for patients who received a RCHOP regimen; there is no statistical difference of the OS between the GCB (88.4%) and the non-GCB group (81.9%, *P*=0.288)

(65.6%) patients younger than 60 years old. The numbers of male and female patients were 128 and 99, respectively. There were 75 (33.0%) patients with B symptoms, and 185 (81.5%) patients had stage III-IV diseases. Sixty-six (29.1%) patients were diagnosed as GCB-like DLBCL, and the other 161 (70.9%) patients were diagnosed as non-GCB DLBCL.

The impact of genetic subtypes on prognosis

Patients were divided into GCB and non-GCB groups according to genetic subtypes, resulting in 66 and 161 patients in each group. The OS in the GCB group (84.8%) was significantly higher than that of the non-GCB group (72.7%, *P*=0.028) (Table 1 and Figure 1A). Patients with different genetic subtypes were further classified according to different therapeutic regimens in order to compare their prognosis. In patients treated with CHOP, the OS in the GCB group (78.3%) was significantly higher than that of the non-GCB group (55.4%, *P*=0.037) (Figure 1B) and in those managed with RCHOP, there was no statistical difference of the OS between the GCB (88.4%) and non-GCB group (81.9%, *P*=0.288) (Figure 1C).

The relationship between extra nodal involvement and prognosis

Patients were classified into primary nodal lymphoma group and extra nodal involvement lymphoma group. Each group had 112 and 115 patients respectively. The OS in the extra nodal involvement lymphoma group (82.6%) was significantly higher than that of the primary nodal lymphoma group (69.6%, *P*=0.033) (Table 1 and Figure 2A). Then we classified patients according to different therapeutic regimens into CHOP and RCHOP groups, and a Kaplan-Meier analysis was performed to investigate the extra nodal involvement in these two groups with different treatments. In patients treated with CHOP, the OS in the primary nodal lymphoma group (51.1%) was significantly lower than that of the extra nodal involvement lymphoma group (78.1%, *P*=0.008) (Figure 2B), while in patients managed with RCHOP, there is was no statistical difference of the OS between the primary nodal lymphoma (83.1%) and extra nodal involvement lymphoma group (84.3%, *P*=0.909) (Figure 2C).

Univariate and multivariate Analysis of prognostic factors for DLBCL patients

A univariate analysis revealed that positive B-symptoms (*P*=0.003), Ann Arbor stages III/IV (*P*=0.008), elevated LDH level (*P*<0.001), elevated β2-M level (*P*=0.014), primary nodal lymphoma (*P*=0.036) and non-GCB subtype (*P*=0.033) were poor prognostic factors for DLBCL patients. A multivariate analysis revealed that elevated LDH levels (HR, 2.791; 95% CI, 1.499-5.199; *P*=0.001) and non-GCB subtype (HR, 2.113; 95% CI, 1.041-1.266; *P*=0.038) were poor prognostic factors for OS (Table 2)

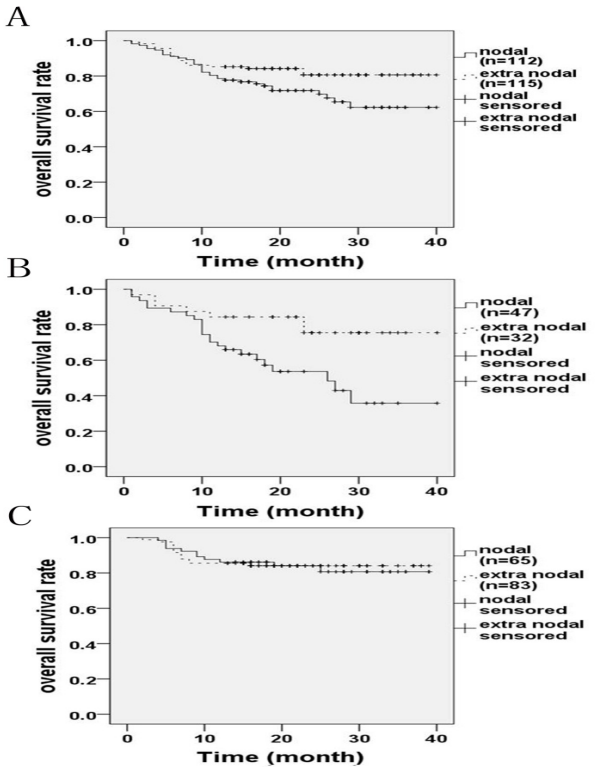

Figure 2. Patients were Classified into Primary Nodal Lymphoma (112 patients) and Extra nodal Involvement Lymphoma (115 patients) Groups. The OS in the extra nodal involvement lymphoma group (82.6%) was significantly higher than that of the primary nodal lymphoma group (69.6%, *P*=0.033). There was no statistical difference of the OS between the primary nodal lymphoma (68.6%) and extra nodal involvement lymphoma group (79.5%, *P*=0.063). Figure 2B. In patients treated with CHOP, the OS in the primary nodal lymphoma group (51.1%) was significantly lower than that of the extra nodal involvement lymphoma group (78.1%, *P*=0.008). Figure 2C. In patients managed with RCHOP; there was no statistical difference of OS between the primary nodal lymphoma (83.1%) and extra nodal involvement lymphoma group (84.3%, *P*=0.909)

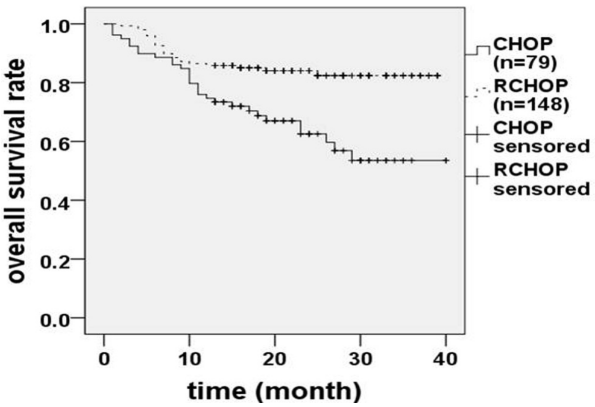

Figure 3. From 227 Patients, 79 were Treated with CHOP and 148 with R-CHOP. The OS in the CHOP group (62.0%) was significantly lower than that of the RCHOP group (83.8%, *P*<0.001)

The impact of Rituximab on prognosis

In 227 patients, 79 cases were treated with CHOP and 148 cases with R-CHOP. The OS in the CHOP group (62.0%) was significantly lower than that of the RCHOP group (83.8%, *P*<0.001) with statistical significance (Table 1 and Figure 3).

Table 3. Cross Prognosis Analysis with Different Prognostic Factors and Chemotherapies

Groups	Regimens	Number of patients	OS	*P* value
LDH>225U/L	CHOP	38	44.70%	*P*=0.022
	RCHOP	63	71.40%	
LDH≤225U/L	CHOP	41	78.00%	*P*=0.018
	RCHOP	85	92.90%	
β2-M>2200μg/L	CHOP	29	51.70%	*P*=0.030
	RCHOP	67	76.10%	
β2-M≤2200μg/L	CHOP	50	68.00%	*P*<0.002
	RCHOP	81	90.10%	
With B symptoms	CHOP	30	40.00%	*P*=0.001
	RCHOP	45	80.00%	
Without B symptoms	CHOP	49	75.50%	*P*=0.174
	RCHOP	103	85.40%	
Primary-nodal lymphoma	CHOP	47	51.10%	*P*<0.001
	RCHOP	65	83.10%	
Extra-nodal lymphoma	CHOP	32	78.10%	*P*=0.537
	RCHOP	83	84.30%	
Ann Arbor stage I/II	CHOP	12	91.70%	*P*=0.750
	RCHOP	30	96.70%	
Ann Arbor stage III/IV	CHOP	67	56.70%	*P*=0.001
	RCHOP	118	80.50%	
IPI=0-1	CHOP	22	95.50%	*P*=0.481
	RCHOP	51	98.00%	
IPI=2	CHOP	20	65.00%	*P*=0.021
	RCHOP	31	90.30%	
IPI=3-5	CHOP	37	40.50%	*P*=0.025
	RCHOP	66	69.70%	
GCB	CHOP	23	78.30%	*P*=0.307
	RCHOP	43	88.40%	
non-GCB	CHOP	56	55.40%	*P*=0.001
	RCHOP	105	81.90%	

OS, overall survival; LDH, lactate dehydrogenase; β2-M, β2-microglobulin; IPI, international prognostic index; GCB, germinal center B-cell-like; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; RCHOP, Rituximab plus CHOP

We regrouped all patients according to the regimens of their chemotherapy in order to analyze the impact of Rituximab in patients with different clinical prognostic factors (Table 3). According to the results, it appeared that in most of the subgroups, patients managed with RCHOP had significantly higher OS when compared with those treated with CHOP, but with several exceptions in some subgroups. In patients without B symptoms, with extra nodal involvement, the genetic subtype GCB, Ann Arbor stage I/II or with an international prognostic index (IPI) score of 0-1, there were no statistical difference between RCHOP and CHOP treatment outcomes.

Discussion

DLBCL is the most common type of NHL in adults with a high clinical heterogeneity and many studies have tried to find useful prognostic factors to guide a treatment. In this research, we examined several markers in 227 patients with DLBCL enrolled in our hospital, and analyzed the impact of age, gender, LDH, β2-M, B symptoms, extra nodal involvement, Ann Arbor stage and

genetic subtypes on the prognosis.

It had been reported by previous researches that when treated with RCHOP, DLBCL patients with extra nodal involvement had a relatively better prognosis when compared with those who did not have extra nodal involvement (Li et al., 2012). We did a similar analysis, but our result was interestingly reverse. In our patients with DLBCL, when treated with CHOP, the OS in the primary nodal lymphoma group (51.1%) was significantly lower than that of the extra nodal involvement lymphoma group (78.1%, P=0.008), while when managed with RCHOP, there was no statistical difference of the OS between primary nodal lymphoma (83.1%) and the extra nodal involvement lymphoma group (84.3%, P=0.909). Since our results were in contrary with other research, we need to cumulate more data to substantiate our finding in future clinical practice.

Our results coincide well with previous researches concerning LDH, β2-M, B symptoms and Ann Arbor stage. All these factors can well predict the prognosis of patients, and were statistically relevant for the OS and it confirms that clinicians should measure these factors in patients with DLBCL in order to better evaluate their prognosis thereby considering stronger regimens for those with poor prognosis.

There have been considerable reports on the relationship between genetic subtype and prognosis, with the well-accepted result that when treated with CHOP, patients with non-GCB DLBCL have a poorer outcome than those with GCB-like DLBCL (Bodoor et al., 2012). Another research also revealed that GCB-like DLBCL shows better response to CHOP regimen (Hassan et al., 2012). However, other researches demonstrated that patients with GCB had a better prognosis than those with non-GCB even when treated with RCHOP (Alizadeh et al., 2000). Here we retrospectively reviewed the predicting significance of genetic subtypes on prognosis. Firstly, when therapeutic regimens were not taken into account, the OS of the GCB group (82.2%) was significantly higher than that of the non-GCB group (70.8%, P=0.035). Then we classified these patients and evaluated the prognosis according to both genetic subtypes and therapeutic regimens. In patients treated with CHOP, the OS in the GCB group (78.3%) was significantly higher than that of the non-GCB group (55.4%, P=0.037). And in patients managed with RCHOP, there was no statistical difference of the OS between the GCB (88.4%) and non-GCB group (81.9%, P=0.288). In summary our research demonstrated that based on the Chinese population, patients with GCB had a better prognosis than those with non-GCB when treated with CHOP, while under the management of RCHOP, there was no statistical OS difference between GCB and non-GCB patients.

In our research, we also retrospectively compared the OS in patients managed with CHOP and RCHOP according to the prognostic grouping of LDH, β2-M, Ann Arbor stage, B symptoms, extra nodal involvement and genetic subtypes. Our results indicated that in most of the subgroups, patients managed with RCHOP had significantly higher OS when compared with those treated with CHOP. But there were also several exceptions in some subgroups. In patients without B symptoms, with extra nodal involvement, the genetic subtype GCB, Ann Arbor stage I/II or an IPI score of 0-1, there were no statistical difference between patients managed with RCHOP and those with CHOP and RCHOP did not improve the prognosis in these patients. The probable reason is: these patients were with relatively low risk, and the OS under the management with CHOP was considerably high during our follow-up while the addition of Rituximab could not improve the prognosis dramatically. So, our research firmly confirmed the historical significance of Rituximab in improving the prognosis of patients with DLBCL.

In summary, this study demonstrated that LDH, β2-M, B symptoms, Ann Arbor stage and genetic subtype can predict the prognosis of Chinese patients with DLBCL. Rituximab combined with chemotherapy provided a better outcome in Chinese patients with DLBCL, but in patients without B symptoms, with extra nodal involvement, the genetic subtype GCB, Ann Arbor stage I/II or an IPI score of 0-1, there were no statistical difference between patients managed with RCHOP and those with CHOP.

In conclusion: This study demonstrated that LDH, β2-M, B symptoms, Ann Arbor stage and genetic subtype can predict the prognosis of Chinese patients with DLBCL. Patients with GCB-like DLBCL have a better prognosis than those with non-GCB when treated with CHOP regimen. Rituximab combined with CHOP chemotherapy provided a better outcome in Chinese patients with DLBCL, but in patients without B symptoms, with extra nodal involvement, the genetic subtype was GCB, Ann Arbor stage was I/II or the IPI score was 0-1, there were no statistical difference between patients managed with RCHOP and those with CHOP.

Acknowledgements

This work was supported by the Research Plan of Medical Science of Health Administration of Zhejiang, China (2012KYB078).

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