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Original Article

Germinal-center type B-cell classification and clinical characteristics of Chinese pediatric diffuse large B-cell lymphoma: a report of 76 cases

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Abstract

Pediatric diffuse large B-cell lymphoma (DLBCL) is a highly aggressive disease with unique clinical characteristics. This study analyzed the germinal-center type B-cell (GCB) classification and clinical characteristics of Chinese pediatric DLBCL. A total of 76 patients with DLBCL newly diagnosed in Sun Yat-sen University Cancer Center between February 2000 and May 2011, with an age younger than 18 years, were included in the analysis. The male/female ratio was 3.47:1. The median age was 12 years (range, 2 to 18 years), and 47 (61.8%) patients were at least 10 years old. Of the 76 patients, 48 (63.2%) had stage III/IV disease, 9 (11.8%) had bone marrow involvement, 1 (1.3%) had central nervous system (CNS) involvement, and 5 (6.6%) had bone involvement. The GCB classification was assessed in 45 patients: 26 (57.8%) were classified as GCB subtype, and 19 (42.2%) were classified as non-GCB subtype. The modified B-NHL-BFM-90/95 regimen was administered to 50 patients, and the 4-year event-free survival (EFS) rate was 85.8%. Among these 50 patients, 31 were assessed for the GCB classification: 17 (54.8%) were classified as GCB subtype, with a 4-year EFS rate of 88.2%; 14 (45.2%) were classified as non-GCB subtype, with a 4-year EFS rate of 92.9%. Our data indicate that bone marrow involvement and stage III/IV disease are common in Chinese pediatric DLBCL patients, whereas the percentage of patients with the GCB subtype is similar to that of patients with the non-GCB subtype. The modified B-NHL-BFM-90/95 protocol is an active and effective treatment protocol for Chinese pediatric patients with DLBCL.

Key words Non-Hodgkin' s lymphoma, diffuse large B-cell lymphoma, pediatric, chemotherapy, germinal-center type B-cell classification, clinical characteristics

Pediatric diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma, accounting for approximately 10%–20% of pediatric non-Hodgkin's lymphomas (NHLs)[1-3]. At present, the best protocols for pediatric mature B-cell lymphomas are B-NHL-BFM-90/95[2,3] and LMB-89/96[4,5]. The event-free survival (EFS) rate of pediatric DLBCL patients treated with the B-NHL-BFM-90/95 protocol has been reported to reach 85%–90%[2,3].

The germinal-center type B-cell (GCB) classification has been used in adult DLBCL to evaluate the prognosis and conduct treatment. Some researchers have used DNA microarrays and immunohistochemistry to divide DLBCL into 3 subtypes according to the immunophenotype and gene expression: germinal-center B-cell–like (GCB) DLBCL, activated B-cell–like (ABC) DLBCL, and type 3 DLBCL (the last two are always called non-GCB subtype)[6-8]. Clinical studies have demonstrated that the prognosis of the GCB subtype is better than that of the non-GCB subtype. Recently, many researchers have considered the GCB classification to have great importance in the clinical treatment of DLBCL[8-13], although others have suggested that the classification has no importance on the prognosis[14-17]. Most likely, the prognostic value of the GCB classification is associated with several factors, including race, age, and treatment. However, the GCB classification and its prognostic value in pediatric DLBCL patients have only been examined by the German Berlin-Frankfurt-Münster (BFM) multicenter trial[18] and French-American-British (FAB) international study group[19]. They have reported that the

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GCB classification has no statistical importance in the prognosis of pediatric DLBCL in Western popula-tions. To date, the clinical characteristics and GCB classification of Chinese pediatric DLBCL patients have not been reported.

Pediatric DLBCL is highly aggressive and has unique clinical characteristics and treatment. In this study, we analyzed the clinical data of 76 pediatric DLBCL patients in Sun Yat-sen University Cancer Center and summarized their clinical characteristics and GCB classifications.

Materials and Methods

Clinical data

Pediatric DLBCL patients who had been treated in Sun Yat-sen University Cancer Center between February 2000 and May 2011 were included into this analysis. All patients were $\leqslant$ 18 years of age and had no history of chemotherapy.

Immunohistochemistry

Immunohistochemical staining and the GCB subtype classification were performed according to the report of Hans *et al*.[8], using the mouse anti-human antibodies CD10 (Zhongshan, 1:50), BCL-6 (Zhongshan, 1:50), and MUM-1 (Dako, 1:50). The Dako detection reagent was used according to the protocol for the Dako Envision system. CD10 was considered positive when membrane staining was observed in $\geqslant$ 30% of tumor cells. MUM-1 and BCL-6 were considered positive when nuclear staining was observed in $\geqslant$ 30% of tumor cells. Cases were classified as GCB subtype when they were $CD10^+$ or $BCL\text{-}6^+MUM\text{-}1^-$; otherwise, they were classified as non-GCB subtype. The mouse anti-human antibody BCL-2 (Dako, 1:50) was also used, and BCL-2 was considered positive when membrane staining was observed in $\geqslant$ 50% of tumor cells.

Staging system

The St. Jude Staging system was adopted[20]. In this staging system, stage IV was defined as tumors involving the bone marrow and/or the central nervous system (CNS), regardless of other sites of involvement. We made a slight modification and defined stage 4 as tumor involvement in the bone marrow, CNS, lung, multiple bones, and liver.

Treatment

Patients were treated with the modified B-NHL-BFM- 90/95 regimen[21,22] alone or in combination with rituximab or radiotherapy; or regimens for adults, e.g., CHOP regimen in combination with rituximab, chemotherapeutic drugs (such as high-dose methotrexate, ifosfamide, cytarabine, and etoposide), radiotherapy, or autologous stem cell transplantation; or tumor resection alone.

Survival analyses

The survival of patients who were treated with the modified B-NHL-BFM-90/95 regimen was analyzed. The period of EFS was defined as the time from diagnosis to the event (treatment failure, death due to tumor or non-tumor reasons), the end of follow-up, or loss to follow-up. The end of follow-up was July 29, 2012.

Statistical analyses

The statistical analyses were performed using SPSS 16.0 statistical software. Differences in measurement data were evaluated using the t test, and differences in categorical data were detected by the χ^2 test or Fisher's exact test, when appropriate. A correlation analysis was performed using the Pearson's correlation. The Kaplan-Meier survival analysis was conducted, and the difference was evaluated using the log-rank test. The significance level was set at α = 0.05 (two-sided).

Results

Clinical characteristics

Between February 2000 and May 2011, 76 pediatric DLBCL patients were treated in Sun Yat-sen University Cancer Center. Of the 76 patients, 59 (77.6%) were males and 17 (22.4%) were females, with a male/female ratio of 3.47:1. The median age was 12 (range, 2–18) years. The median level of lactate dehydrogenase (LDH) was 246.2 U/L (range, 79–2,499 U/L). There were 15 cases (19.7%) with an LDH level $\geqslant$ 500 U/L, 28 (36.8%) stage I/II cases, and 48 (63.2%) stage III/IV cases. The stage was positively correlated with the LDH level (r = 0.326, P = 0.005). The most common sites of tumors were the superficial lymph nodes and the abdominal-pelvic cavity. The detailed clinical characteristics are listed in **Table 1**.

Of the 76 patients, 50 were treated with the modified B-NHL-BFM-90/95 regimen, 24 were treated with regimens for adults, and 2 only underwent tumor resection.

Relationship between GCB subtype and clinical characteristics

The GCB classification was assessed in 45 of the 76 patients, and 26 cases (57.8%) were defined as GCB subtype. Among the 26 cases, 21 expressed CD10. No differences were found in gender, age, risk degree, stage, LDH level, CNS involvement, bone marrow involvement, bone involvement, or extra-nodal involvement between GCB subtype and non-GCB subtype patients (**Table 2**).

Additionally, 42 of the 76 cases were evaluated for BCL-2, and 26 (61.9%) were BCL-2–positive.

Survival analyses

The 50 patients treated with the modified B-NHL-BFM-90/95 regimen were followed up for 4 to 106 months, with a median of 43

Table 1. The clinical characteristics of 76 pediatric patients with DLBCL

Clinical characteristic	Number of patients (%)	Clinical characteristic	Number of patients (%)
Sex		B symptoms	
Male	59 (77.6)	Positive	26 (34.2)
Female	17 (22.4)	Negative	50 (65.8)
Age		Stage	
< 10 years	29 (38.2)	I + II	28 (36.8)
⩾ 10 years	47 (61.8)	III + IV	48 (63.2)
CNS involvement		LDH level	
Positive	1 (1.3)	< 500 U/L	61 (80.3)
Negative	75 (98.7)	⩾ 500 U/L	15 (19.7)
Bone marrow involvement		Extra-nodal involvement	
Positive	9 (11.8)	Yes	63 (82.9)
Negative	67 (88.2)	No	13 (17.1)
Bone involvement		Tumor site	
Positive	5 (6.6)	Superficial lymph nodes	44 (57.9)
Negative	71 (93.4)	Abdominal-pelvic cavity	25 (32.9)
		Pharynx	17 (22.4)
		Mediastinum	9 (11.8)

CNS, central nervous system; LDH, lactate dehydrogenase.

months. The 4-year EFS rate was 85.8% (**Figure 1A**). Six patients died: 1 died of toxic effects of chemotherapy, 4 died of tumor within 2.5 years, and 1 died of non-tumor factors.

The GCB subtype was assessed in 31 of the 50 patients treated with the modified B-NHL-BFM-90/95 regimen. The 4-year EFS rates of 17 GCB subtype patients and 14 non-GCB subtype patients were similar (88.2% vs. 92.9%, P = 0.671) (**Figure 1B**).

Additionally, 27 of the 50 patients were assessed for BCL-2 expression. No significant difference in the 4-year EFS rate was observed between 17 BCL-2–positive patients and 10 BCL-2–negative patients (88.2% vs. 100%, *P* = 0.271) (**Figure 1C**).

Discussion

Adult and pediatric DLBCL differ in some respects. Adult DLBCL demonstrates clinical, biological, and pathologic heterogeneity[23]. Clinically, the median age of adult DLBCL patients is approximately 60 years; the male/female ratio is approximately 1.5:1; the proportion of stage III/IV (the Ann Arbor Staging system) patients is 44%–52%; the percentage of patients with B symptoms is 24%–31%[24]; and bone marrow involvement is observed in 10%-30% of patients[25,26]. The clinical characteristics of pediatric DLBCL differ from those of adult DLBCL[18,27,28]: the median age of Western pediatric DLBCL patients is 11.4 years (range, 1.4 to 17.9 years)[29]; the percentage of patients ⩾ 10 years old is approximately 60%[18]; the male/female ratio is 2:1; the percentage of patients with stage III/IV (the St. Jude Staging system) is 45%; bone marrow involvement is observed in 1% of patients; CNS involvement in 3%; mediastinal involvement in 14%; bone involvement in 8%; B symptoms in 14%; LDH level ⩾ 500 U/L in 14%; immunodeficiency in 6%[29]; and extra-nodal involvement in nearly 80%[18]. Our study indicated that the median age of Chinese pediatric DLBCL patients was 12 years (range, 2 to 18 years) and the proportion of patients ⩾ 10 years old was 61.8%. Additionally, the percentage of patients with CNS involvement was 1.3%, with mediastinal involvement in 11.8% and bone involvement in 6.6%. These data are similar to those of Western pediatric DLBCL patients. However, the percentage of patients with an LDH level ⩾ 500 U/L (19.7%) was slightly higher, and the percentage of patients with bone marrow involvement (11.8%) and the percentage of patients with stage III/IV disease (63.2%) were significantly higher.

The proportion of GCB subtype disease differed between adult and pediatric DLBCL patients. According to previous studies, the proportion of GCB subtype disease was 30% in Asian patients[30] and 22.1% in Chinese adult DLBCL patients[31], both of which were significantly lower than that observed in Western adult patients (50%)[30]. Additionally, this proportion in Japanese patients younger than 30 years (25%) was also relatively low[32]. The proportion of GCB subtype disease in Chinese patients (75%) has only been reported in one study that included 8 DLBCL patients younger than 13 years[33]. Our retrospective study indicated that the proportion of the GCB subtype in Chinese pediatric DLBCL patients (57.8%) was significantly lower than those in the BFM multicenter trial (82.7%)[18] and the FAB

Table 2. Clinical characteristics of GCB subtype and non-GCB subtype patients

Characteristic	GCB [no. (%)]	non-GCB [no. (%)]	*P*
Sex			0.720
Male	21 (80.8)	14 (73.7)	
Female	5 (19.2)	5 (26.3)	
Age			0.757
< 10 years	10 (38.5)	6 (31.6)	
⩾ 10 years	16 (61.5)	13 (68.4)	
CNS involvement			0.422
Positive	0 (0)	1 (5.3)	
Negative	26 (100)	18 (94.7)	
Bone marrow involvement			0.377
Positive	2 (7.7)	4 (21.1)	
Negative	24 (92.3)	15 (78.9)	
Bone involvement			0.636
Positive	2 (7.7)	3 (15.8)	
Negative	24 (92.3)	16 (84.2)	
Stage			0.757
I/II	10 (38.5)	6 (31.6)	
III/IV	16 (61.5)	13 (68.4)	
LDH level			1.000
< 500 U/L	21 (80.8)	16 (84.2)	
⩾ 500 U/L	5 (19.2)	3 (15.8)	
Extra-nodal involvement			1.000
Positive	22 (84.6)	16 (84.2)	
Negative	4 (15.4)	3 (15.8)	

GCB, germinal-center type B-cell classification. Other abbreviations as in Table 1.

international study (75%)[19]. Additionally, it was significantly higher than that reported for Chinese adult DLBCL patients. The immunohistochemical evaluation of BCL-2 in our study indicated that the proportion of pediatric patients expressing BCL-2 in our center (61.9%) was higher than those in the BFM multicenter trial (40%)[18] and the FAB international study. There is no obvious relationship between clinical characteristics and the GCB classification[34]. Our data showed no difference in sex, age, CNS involvement, bone marrow involvement, bone involvement, stage, LDH level, or extra-nodal involvement between GCB and non-GCB subtype patients, which were similar to those published.

The prognosis of adult GCB subtype DLBCL patients is better than that of non-GCB subtype patients. According to the BFM multicenter trial, there was no significant difference in the 5-year EFS rate between 43 GCB subtype patients and 9 non-GCB subtype patients (93% vs. 89%, $P = 0.6$)[18]. In our study, 50 patients were treated with the modified B-NHL-BFM-90/95 regimen, and the 4-year EFS rate was 88.6%. In 31 of the 50 patients assessed for the GCB classification, there was no significant difference in the 4-year EFS rate between 17 GCB subtype patients and 14 non-GCB subtype patients (88.2% vs. 92.9%, $P = 0.671$). The B-NHL-BFM-90/95 regimen, which is the internationally accepted best therapy for pediatric NHL, is a stratified therapy regimen according to risk factors. Patients with early stage disease are treated with chemotherapy at a lower intensity, whereas patients with late stage disease are treated at a higher intensity. Our data showed that the GCB subtype did not impact the 4-year EFS of Chinese pediatric patients who were previously untreated and were given the modified B-NHL-BFM-90/95 regimen. It is likely that the chemotherapy regimen administered can alter the effect of the GCB classification on DLBCL patient survival.

Additionally, the detection of BCL-2 in the BFM multicenter trial in pediatric DLBCL patients indicated that it was not related to prognosis [18]. Similarly, our data also showed no significant difference in EFS of BCL-2–positive patients and BCL-2–negative patients ($P = 0.271$).

In conclusion, our study showed that Chinese pediatric DLBCL patients presented with a higher proportion of stage III/IV disease and bone marrow involvement and a lower proportion of GCB subtype disease compared to their Western peers. Additionally, the proportion of GCB subtype disease in pediatric patients was significantly higher than that in Chinese adult DLBCL patients. The modified B-NHL-BFM-90/95 regimen could guarantee a promising outcome in Chinese pediatric DLBCL patients. It also appears that the GCB subtype has no effect on Chinese pediatric DLBCL patients treated with the

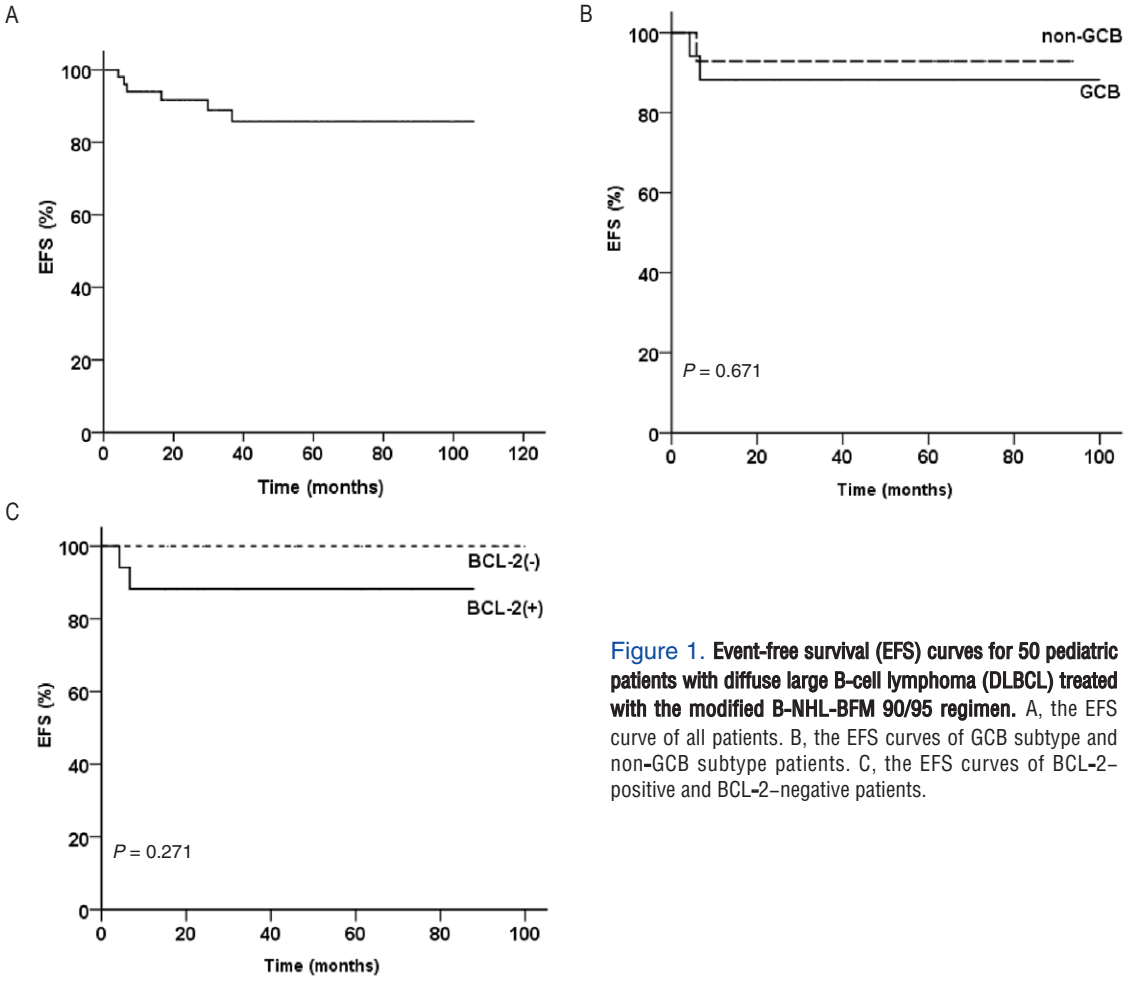

Figure 1. **Event-free survival (EFS) curves for 50 pediatric patients with diffuse large B-cell lymphoma (DLBCL) treated with the modified B-NHL-BFM 90/95 regimen.** A, the EFS curve of all patients. B, the EFS curves of GCB subtype and non-GCB subtype patients. C, the EFS curves of BCL-2–positive and BCL-2–negative patients.

modified B-NHL-BFM-90/95 regimen.

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