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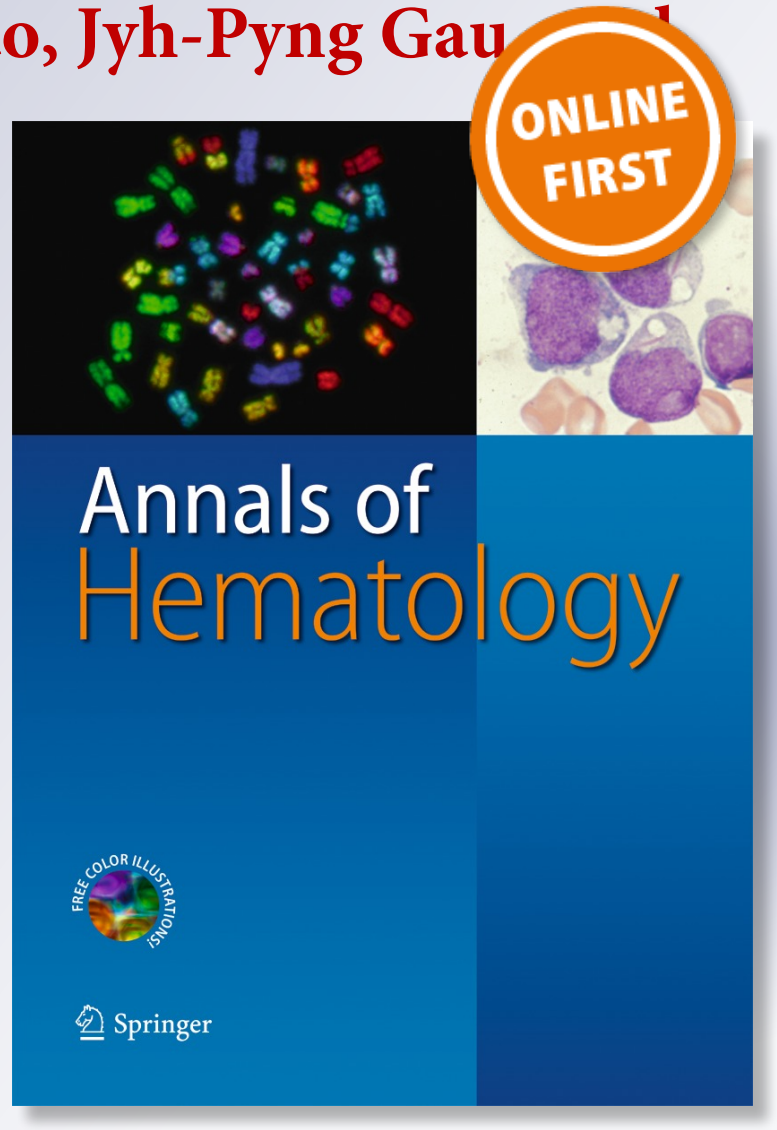

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ORIGINAL ARTICLE

Diminishing prognostic role of preexisting diabetes mellitus for patients with diffuse large B-cell lymphoma in the rituximab era

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Abstract Rituximab reforms the treatment of diffuse large B-cell lymphoma (DLBCL) and the prognostic significance of baseline patient features should be reevaluated. Few population-based studies have investigated the association of diabetes mellitus (DM) and outcomes of lymphoma; however, the results remain inconclusive. From January 1, 2000 to December 31, 2009, a total of 468 consecutive newly diagnosed DLBCL patients receiving first-line chemotherapy with cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP) or rituximab plus CHOP (R-CHOP) were enrolled. Pre-existing DM was defined according to medical history, use of antidiabetic medications, or any record of an abnormal hemoglobin A1c test. Progression-free survival (PFS) and overall survival (OS) were estimated and compared using the Kaplan–Meier method with a log-rank test. CHOP was administered in 194 patients, and 274 patients received R-CHOP. DM was identified in 16.2 % (76/468) of patients. Diabetic patients were older and more performance restricted, compared to the non-DM patients in both the CHOP and R-CHOP groups. In the CHOP group, 5-year PFS and OS were inferior in DM patients (PFS, 32.4 vs. 50.0 % (P=0.039); OS, 38.2 vs. 62.5 % (P=0.002)). However, outcomes were similar

H.-J. Lu and Y.-C. Huang equally contributed to this work.

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for both DM and non-DM patients in the context of R-CHOP treatment (PFS, 69.0 vs. 57.3 % (P=0.179); OS, 76.2 vs. 69.8 % (P=0.586)). The response rate of chemotherapy in DM patients was also improved to a level similar to non-DM patients with rituximab use. In conclusion, the prognostic significance of preexisting DM in DLBCL patients is changing in the rituximab era. The potentially additional benefit of rituximab in DM patients merits further investigation.

Keywords Diabetes mellitus · Diffuse large B-cell lymphoma · Prognosis · Rituximab

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin's lymphoma (NHL). For decades, the standard front-line chemotherapy for DLBCL has been a regimen consisting of cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP) [1]. The International Prognostic Index (IPI), which was developed in 1993 and consists of five clinical parameters, has been widely applied to predict the outcome of patients with DLBCL [2]. However, the introduction of rituximab in the past decade has reformed the treatment of DLBCL, and the integration of rituximab in front-line and salvage settings has significantly improved survival outcomes [3]. Recently, revisions of IPI have also been suggested in response to the various prognoses in the rituximab era [4–6]. In addition, several lines of evidence show that rituximab alters the prognostic values of clinical and molecular surrogates [7, 8]. Therefore, prognostic factors in the prerituximab era might warrant re-evaluation in the contemporary treatment paradigm [9].

Diabetes mellitus (DM), a common comorbid disease, affects an estimated 3–4 % of the general population [10]. Epidemiologic evidence suggests an association between DM and increased risk of several types of cancers [11, 12], and systematic review further shows that cancer patients with preexisting DM are at a higher risk of all-cause mortality compared with those without DM [13–15]. Recent meta-analysis reports a positive association between DM and the risk of NHL, although this remains relatively controversial. However, the evidence regarding the effect of preexisting DM on lymphoma outcomes remains limited and inconclusive [13, 15–18]. In addition, no study has investigated the possible interactions of DM and the treatment paradigm shift caused by rituximab.

This study presents an investigation of the prognostic effect of preexisting DM on patients with DLBCL, instead of all NHL cases, which represent considerably more heterogeneous populations. This study also presents a comparison of patients in prerituximab and rituximab eras to determine the possible modulation effects of rituximab on the role of preexisting DM in DLBCL.

Patients and methods

Study population and data collection

Patients who were newly diagnosed CD20-positive DLBCL between January 1, 2000 and December 31, 2009 were retrospectively enrolled in the study. Patients were eligible for inclusion if they were treated with first-line CHOP or R-CHOP protocols. To clearly separate the patients receiving rituximab-containing regimens from those without, the patients who received rituximab salvage therapy were excluded from the CHOP group. Patients were ineligible for inclusion if they had primary central nervous system involvement or human immunodeficiency virus infection. All patients were staged according to the clinical practice guidelines and the baseline characteristics of patients were collected at the time of diagnosis [19, 20]. Follow-up was continued until December 31, 2011 or the time of death. This study was reviewed and approved by the Institutional Review Board of Taipei Veterans General Hospital.

Definition of preexisting DM

Patients were defined as having preexisting diabetes if they had any one of the following characteristics at the time of diagnosis: discharge diagnosis of diabetes for any previous hospitalization, records of diabetes at two or more outpatient visits, usage of any antidiabetic medication, or a record of an abnormal hemoglobin A1c test (>6.7 %) [21, 22].

Treatment

Reimbursement for front-line rituximab in DLBCL has been approved by the Bureau of National Health Insurance of Taiwan since December 2003. For this reason, most patients diagnosed during the period from 2000 to 2003 received first-line chemotherapy without the addition of rituximab. In contrast, most of those diagnosed after 2004 received chemotherapy combined with rituximab. The CHOP dosing schedule was provided as described previously [3, 20, 23]. For elderly patients considered to have borderline cardiac function, the dosage of doxorubicin was modified or replaced with epirubicin, producing CHOP-like regimens. The decisions for second-line treatment were made on an individual basis at the discretion of the attending physicians. Autologous stem cell transplantation was performed in patients with an adequate peripheral stem cell harvest and suitable clinical conditions after second-line chemotherapy [23].

Response evaluation

Response was evaluated according Cheson's criteria [24]. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of documented PD or death from any cause. Overall survival (OS) was calculated from the date of diagnosis to the date of death by any cause or last follow-up. After therapy, CT scans were performed every 3 or 6 months over the following 2 years and then annually until 5 years after the completion of therapy.

Statistical analysis

Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the Mann–Whitney *U* test. Survival curves were calculated according to the Kaplan–Meier method and compared using the log-rank test. We analyzed the effect of preexisting DM for OS after IPI adjustment using multivariate Cox proportional hazard regression. In all analyses, a two-sided *P* value of <0.05 was regarded as statistically significant, and we performed all statistical analysis using SPSS statistical software version 19.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

The sample in this study consists of 468 patients diagnosed with DLBCL between January 2000 and December 2009. Among them, 194 patients were treated with CHOP (primarily from 2000 to 2003) and 274 patients were treated with R-CHOP (primarily from 2004 to 2009). The median age in the CHOP group was 64.5 years (range, 12–-91 years), and 66.0 % of the patients were male. The median follow-up was 39.6 months (range, 0.4–143.0 months). The median age in the R-CHOP group was 69.5 years (range, 16–88 years), and 59.1 % of the patients were male. The median follow-up was 34.4 months (range, 0.5–111.2 months). The 5-year PFS and OS outcomes were better in the R-CHOP group than the CHOP group (5-year PFS, 59.1 vs. 46.9 % (*P*=0.001); 5-year OS, 70.8 vs. 58.2 % (*P*=0.005)).

Seventy-six patients (16.2 %) were identified as preexisting DM. Thirty-four of these patients (17.5 %) were in the CHOP group, and the remaining 42 patients (15.3 %) received first-line treatment with R-CHOP. Table 1 presents a summary of the clinical characteristic of both groups. The DM patients in

Table 1 Patient characteristics of first-line CHOP±rituximab

	CHOP (*n*=194)			R-CHOP (*n*=274)		
	Non-DM (*n*=160)	DM (*n*=34)	*P*	Non-DM (*n*=232)	DM (*n*=42)	*P*
Gender						
Male	107 (66.9 %)	21 (61.8 %)	0.351	135 (58.2 %)	27 (64.3 %)	0.287
Female	53 (33.1 %)	13 (38.2 %)		97 (41.8 %)	15 (35.7 %)	
Age						
≦60	78 (48.8 %)	7 (20.6 %)	0.002	94 (40.5 %)	4 (9.5 %)	<0.001
>60	82 (51.3 %)	27 (79.4 %)		138 (59.5 %)	38 (90.5 %)	
PS						
≦1	107 (66.9 %)	15 (44.1 %)	0.012	163 (70.3 %)	22 (52.4 %)	0.020
>1	53 (33.1 %)	19 (55.9 %)		69 (29.7 %)	20 (47.6 %)	
LDH						
≦ULN	58 (36.3 %)	12 (35.3 %)	0.541	74 (31.9 %)	14 (33.3 %)	0.492
>ULN	102 (63.8 %)	22 (64.7 %)		158 (68.1 %)	28 (66.7 %)	
Stage						
≦2	90 (56.3 %)	20 (58.8 %)	0.469	107 (46.1 %)	19 (45.2 %)	0.526
>2	70 (43.8 %)	14 (41.2 %)		125 (53.9 %)	23 (54.8 %)	
Extranodal site(s)						
≦1	136 (85.0 %)	28 (82.4 %)	0.434	176 (75.9 %)	32 (76.2 %)	0.569
>1	24 (15.0 %)	6 (17.6 %)		56 (24.1 %)	10 (23.8 %)	
IPI score						
Low	64 (40.0 %)	10 (29.4 %)	0.316	76 (32.8 %)	8 (19.0 %)	0.164
Low intermediate	35 (21.9 %)	6 (17.6 %)		43 (18.5 %)	10 (23.8 %)	
High intermediate	31 (19.4 %)	7 (20.6 %)		59 (25.4 %)	9 (21.4 %)	
High	30 (18.8 %)	11 (32.4 %)		54 (23.3 %)	15 (35.7 %)	

CHOP cyclophosphamide, doxorubicin, vincristine and prednisolone; *R* rituximab; *DM* diabetes mellitus; *PS* performance status; *LDH* lactate dehydrogenase; *ULN* upper limit of normality; *IPI* International Prognostic Index

the CHOP group were older and more performance-restricted compared to the non-DM patients (age, >60 years; 79.4 vs. 51.3 % (P=0.002); PS ECOG, >1; 55.9 vs. 33.1 % (P=0.012)). Similarly, the DM and non-DM patients in the R-CHOP group exhibited significant differences in age and PS (age, >60 years; 90.5 vs. 59.5 % (P<0.001); PS ECOG, >1; 47.6 vs. 29.7 % (P=0.020)). Otherwise, other clinical parameters, including gender, lactate dehydrogenase, Ann Arbor stage, involvement of extranodal sites, and risk stratification by IPI, were not significantly different among the DM and non-DM patients in both groups.

Because DLBCL patients in the rituximab era were diagnosed 1–9 years after those diagnosed in the prerituximab era, a difference in the clinical characteristics of DM patients might exist. To this end, this study presents a comparison of the baseline laboratory parameters, glycemic control modalities, and associated comorbidities of DM patients in both groups (Electronic supplementary material Table 1). All of the investigated characteristics were similar in both groups of DM patients. No major complications, such as cardiovascular events or hyperosmolar hyperglycemic state, occurred during the course of first-line chemotherapy in both groups of DM patients.

Impact of preexisting DM on survival outcomes in DLBCL patients

This study presents a comparison of the outcomes of patients with or without DM in both CHOP and R-CHOP groups. In the CHOP group, DM patients had worse PFS and OS compared to non-DM patients (5-year PFS, 32.4 vs.50.0 % (P=0.039); 5-year OS, 38.2 vs. 62.5 % (P=0.002; Fig. 1)). However, the survival outcomes of DM and non-DM patients were not significantly different when they were treated with first-line rituximab and CHOP (5-year PFS, 69.0 vs. 57.3 % (P=0.179); 5-year OS, 76.2 vs. 69.8 % (P=0.586; Fig. 2)). After adjusting for the IPI score using the Cox proportional hazard regression, preexisting DM remained an independently poor prognostic factor for OS [hazard ratio (HR), 1.82; 95 % confidence interval (CI), 1.11–2.98, P=0.017] in the CHOP group. In contrast, DM was not a prognostic factor for OS in patients receiving rituximab-containing treatment after risk adjustment (HR 0.73, 95 % CI, 0.38–1.42; P=0.358).

The treatment response of first-line chemotherapy is strongly associated with survival outcomes [23]. Therefore, we assessed the response rates of DM and non-DM patients in both CHOP and RCHOP groups. As Table 2 shows, the overall response rate (ORR) was 74.2 % in the CHOP group, including a 44.3 % CR rate. The response rate was significantly lower in DM patients compared to non-DM patients (ORR, 57.7 %; CR, 34.6 vs. 77.3 and 46.1 % (P=0.035)). In patients receiving R-CHOP, the ORR improved to 92.4 %, including a 64.0 % CR rate. In addition, there was no significant difference in the response rate of DM and non-DM patients (ORR, 92.3 %; CR, 74.4 vs. 92.3 and 62.1 % (P=0.600)).

Discussion

Numerous studies have explored the association between DM and cancer. The relative risks are greatest for cancers of the liver, pancreas, and endometrium [11, 12]. The results of some, but not all, epidemiological studies also indicate that DM may increase mortality in cancer patients [13–15, 25–27]. However, this conclusion is controversial for other cancers, such as NHL [11, 12, 16, 28]. Three recent meta-analyses suggest that DM is associated with a moderately increased risk of NHL [17, 29, 30], but the results for NHL

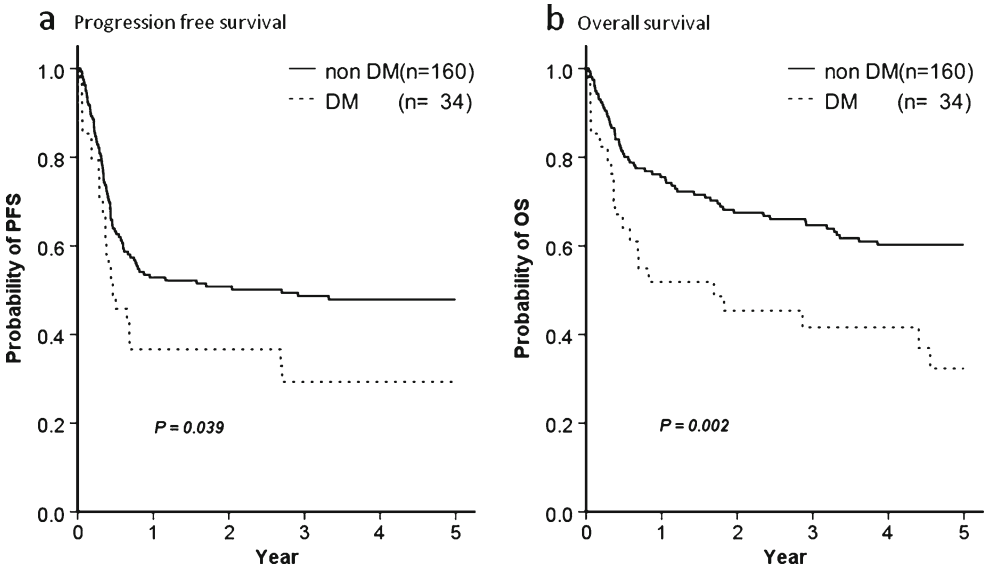

Fig. 1 Progression-free survival and overall survival of patients with or without DM who received CHOP. The DM patients had lower PFS and OS than non-DM patients. **a** Five-year PFS, 32.4 vs. 50.5 % (P=0.039); **b** 5-year OS, 38.2 vs. 62.5 % (P=0.002)

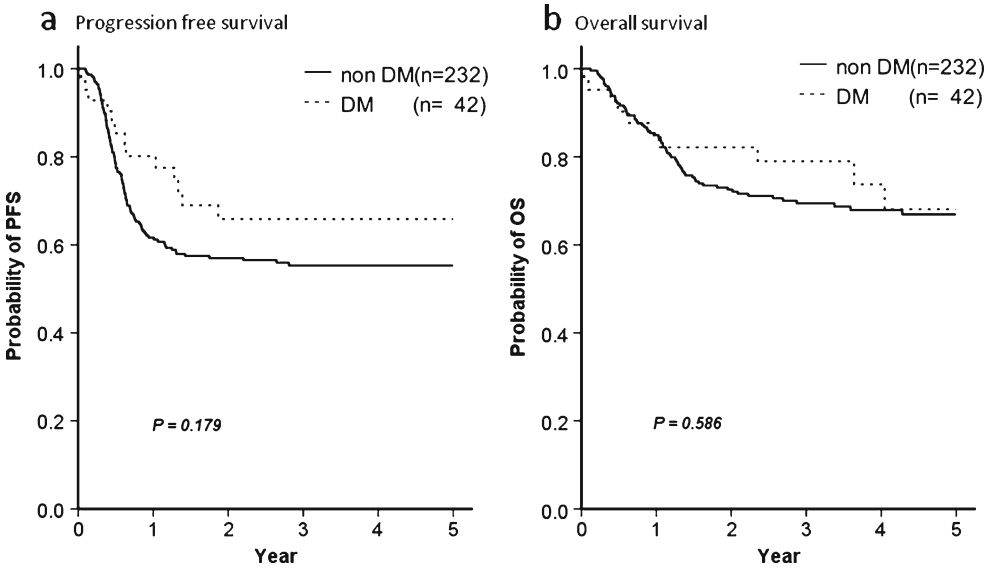

Fig. 2 Progression-free survival and overall survival of patients with or without DM who received R-CHOP. The DM and non-DM patients exhibited no significant differences in survival outcomes. **a** Five-year PFS, 69.0 vs. 57.3 % (P=0.179); **b** 5-year OS, 76.2 vs. 69.8 % (P=0.586)

subtypes vary [30]. In addition, research on the effects of DM on NHL prognosis remains limited. Coughlin et al. enrolled 1,560 patients diagnosed with NHL from 1980 to 1998 and revealed that the HR was 1.21 (95 % CI, 0.99–1.48) for mortality [13]. Similarly, a study by Lin et al. shows no significant difference in OS between DM and non-DM patients who were diagnosed NHL from 2000 to 2004 (relative risk, 1.33; 95 % CI, 0.61–2.90) [16]. Using a population-based approach, Tseng et al. recently reported that DM patients have a higher risk of mortality from NHL, but they failed to define the prognostic role of DM on NHL [31]. In addition to the controversy between these studies, it is difficult to apply these results to the clinical prediction of prognosis on specific lymphoma subtypes because NHL consists of a very heterogeneous group of diseases. By focusing on DLBCL, the most common subtype of NHL, this study shows that DM is a poor prognostic factor with independence of IPI in patients receiving CHOP induction therapy. However, the negative effect of DM is no longer present in patients receiving rituximab-containing induction regimen. To the best of our knowledge, this is the first study to investigate the effect of DM on the survival outcomes of a specific subtype of lymphoma in both prerituximab and rituximab eras. Despite its retrospective study design, this study provides consolidated evidence based on a large consecutive cohort of patients with specific diagnosis of DLBCL and relatively uniform treatment protocols.

The explanations of the prognostic effects mediated by diabetes for patients with DLBCL remain unclear. Recent evidence suggests that inflammation participates in the pathogenesis of type 2 diabetes [32, 33]. Type 2 DM patients have elevated levels of circulating proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor. Metabolic stress activates IκB kinase-β (IKKβ) and JUN N-terminal kinase (JNK), leading to the transactivation of the nuclear factor-κB (NF-κB) pathway and subsequent proinflammatory response. Similarly, the activated B cell-like subtype of DLBCL, which typically has a poorer prognosis, exhibits the constitutive activation of IKK [34, 35]. IKK phosphorylates the IκB family, and subsequent degradation of IκB leads to the release of NF-κB family members and activates transcription mediating proliferation, apoptosis, and cell survival. Bavi et al. further demonstrated that NF-κB overexpression is an independent prognostic marker

Table 2 The response of treatment for patients with first-line CHOP±rituximab

Response, n (%)		CHOP (n=167)				R-CHOP (n=261)		
	Overall	Non-DM (n=141)	DM (n=26)	P	Overall	Non-DM (n=222)	DM (n=39)	P
CR	74 (44.3)	65 (46.1)	9 (34.6)	0.035	167 (64.0)	138 (62.1)	29 (74.4)	0.600
PR	50 (29.9)	44 (31.2)	6 (23.1)		74 (28.4)	67 (30.2)	7 (17.9)	
Stable disease	3 (1.8)	3 (2.1)	0 (0.0)		2 (0.8)	1 (0.5)	1 (2.6)	
Progressive disease	40 (24.0)	29 (20.6)	11 (42.3)		18 (6.9)	16 (7.2)	2 (5.1)	

Forty patients could not be assessed: 24 patients died before restaging, 16 patients lost follow-ups

CHOP cyclophosphamide, doxorubicin, vincristine and prednisolone; *DM* diabetes mellitus; *CR* complete remission; *PR* partial remission

for poor survival in DLBCL and inhibition of NF-κB expression in vitro downregulates downstream target gene products, such as Bcl-2, Bcl-x_L, and survivin, leading to apoptosis [36]. Rituximab has several potential mechanisms of action, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and the induction of apoptosis [37]. Jazirehi et al. demonstrated that rituximab also inhibits the constitutive NF-κB activity that regulates Bcl-x_L expression. This inhibition by rituximab sensitizes B cells to chemotherapeutic drug-induced apoptosis [38]. Gupta et al. showed that anti-CD20 humanized antibodies alter multiple signaling pathways, including a significant reduction in the phosphorylation of IKKα/β and IκBα, ultimately leading to cell death [39]. These data provide a possible explanation for the benefits of rituximab in DLBCL patients with diabetes and support the observation that response rate and survival outcomes of patients with DM are markedly improved after receiving rituximab-containing regimens. There were some limitations to this study. First, to enroll patients treated with relatively uniform treatment protocols, we recruited only patients treated with first-line CHOP or R-CHOP regimens. Therefore, patients of extremely old age or poor performance might not be analyzed in this study. In another word, our conclusion regarding the effect of DM on DLBCL is only applicable to the intent-to-treat population. In addition, the small number of diabetic patients might have prevented this study from detecting a statistically significant difference in the survival rates of diabetic and nondiabetic patients. Furthermore, other than using rituximab, periodic effects, such as the improvement of supportive care, could not be excluded as causes that modulate the role of diabetes in DLBCL patients. Second, because of the retrospective design of this study, patients with preexisting DM were identified based on various medical records, including laboratory data, diabetes medication prescriptions, and medical charts. In this study, 31 patients (40.8 %) were diagnosed with DM based on pretreatment laboratory examinations. Although the diagnosis of DM is not straightforward, a large registry, Kaiser Permanente Northern California Diabetes Registry [21, 25], adopts the same criteria. This registry, which was established in 1993 and annually identifies prevalent and incident cases of diabetes using these criteria, is 99.5 % sensitive with a 2 % false-positive rate for diagnosed diabetes as of January 2003 [21, 25, 40]. These data suggest the adequacy of using these criteria in this retrospective study. Finally, because of the limitations of study design, serial follow-up of relevant laboratory data for diabetes was not routinely available in our study. Although the patients in this study had no recorded major cardiovascular or hyperglycemic events, a prospective study is necessary to investigate the alterations of glycemic control if it is modulated with the introduction of rituximab.

In conclusion, this study shows the effects of preexisting DM on patients with DLBCL. In patients not exposed to rituximab, DM is an independent poor prognostic factor. However, the negative role of DM is diminishing in the rituximab era. The significant improvement of treatment response in DM patients might be one of the reasons for the prognostic changes, but the exact mechanism of the alterations remains unclear. Thus, the potentially additional benefit of rituximab in DM patients warrants further investigation.

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