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Research Article
NF-κB Signaling Pathway and Efficacy of Bortezomib-Based Combination Chemotherapy in Patients with Non-Hodgkin's Lymphoma

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Abstract

Background and Objective: The efficacy of bortezomib-based chemotherapy on Non-Hodgkin's Lymphoma (NHL) patients has been a controversial question. Therefore, in this study, we evaluated whether a different efficacy of chemotherapy in patients with a variety of NHL subtypes. **Materials and Methods:** We reviewed the electronic medical records of West China Hospital of Sichuan University from January, 2004-2014 and included 48 NHL patients treated with at least two cycles of bortezomib-based chemotherapy. **Results:** On immunostaining, 18 (35.7%) and 16 (33.3%) presented p65 and RelB nuclear staining patterns, respectively. After treatment, 4 patients (13.3%) with p65-negative were complete remission and 8 (44.4%) with p65-positive were complete remission. The complete remission rate in patients with p65-positive was higher than those with negative ($p<0.0001$). NF-κB-activated p65 was related to a high rate of complete remission (OR: 4.80, 95% CI: 1.173, 19.6) for bortezomib treatment, the activated Relb was related with a high risk of inefficacy (OR: 0.045, 95% CI: 0.05, 0.395) for bortezomib treatment. NF-κB and Relb activation should be monitored for helping bortezomib therapy selection. **Conclusion:** We found that the positive expression of p65 after nuclear staining and the negative expression of RelB after nuclear staining tended to indicate an effective treatment of bortezomib-based combination chemotherapy. However, due to the limited number of participants, further large scale, well-designed, prospective studies are warranted to confirm our findings.

Key words: NF-κB, lymphoma, non-Hodgkin, bortezomib, immunohistochemistry, treatment outcome, pathological studies

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Non-Hodgkin's Lymphoma (NHL), a heterogeneous group of lymphoid malignancies, presents an important clinical challenge. Many patients who undergo treatment with a conventional CHOP or CHOP-based regimen relapse or cannot successfully achieve remission. Recently, a series of basic studies found that the Nuclear Factor-κB (NF-κB) signalling pathway can be activated inappropriately in NHL patients, which suggests that activation of the NF-κB signalling pathway may play a key role in oncogenesis and the progression of lymphoid malignancies[1-5]. The NF-κB signalling pathway is a small family of inducible transcription factors and exists in virtually all mammalian cells[6]. Currently, a total of five subunits of NF-κB have been reported: RelA (p65), RelB, c-Rel, NF-κB1 (p50 and its precursor p105) and NF-κB2 (p52 and its precursor p100). There are several explanations for the anticancer properties of bortezomib. The key mechanism is its inhibition of IκB degradation, leading to the maintenance of NF-κB in the cytoplasm, thereby reducing NF-κB activity[7,8]. Interestingly, these clinical trials demonstrated different levels of bortezomib's efficacy within various subtypes of NHL.

Therefore, we observed 48 NHL patients treated with at least two cycles of bortezomib-based combination chemotherapy and evaluate whether a different efficacy of chemotherapy in patients with a variety of NHL subtypes.

MATERIALS AND METHODS

Study area: This study was carried out at the West China Hospitalof Sichuan University, Chengdu in China, from September, 2011-2014.

Data collection: Patients who suffered from non-Hodgkin's lymphoma and underwent at least two cycles of standard bortezomib-based combination chemotherapy for about 6-8 weeks of treatment were included in this study. We reviewed the electronic medical records of West China Hospital from January, 2004-2014 and a total of 48 patients were ultimately enrolled, including 25 relapsed/refractory Diffuse Large B-Cell Lymphoma (DLBCL), 6 relapsed/refractory Follicular Lymphoma (FL), 4 newly diagnosed Mantle Cell Lymphoma (MCL) and 4 relapsed/refractory Mantle Cell Lymphoma (MCL), 9 relapsed/refractory Peripheral T-Cell Lymphoma (PTCL).

Ethical approval: The study was approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee (2019 Review (No.618).

Methodology: Paraffin-embedded tissue blocks from NHL biopsy specimens were retrieved from the pathological archives of our hospital. The pathological records of all these cases were reviewed and the pathological diagnoses were confirmed following the criteria of the World Health Organization classification (2008 edition). Standard immunohistochemistry was carried out with a biotin-free EnVision kit (Dako). The rabbit monoclonal antibodies for NF-κB and RelB were purchased from Abcam (Abcam, UK). Tissue sections probed with normal IgG were used as a negative control. Ten random microscope fields with 400× magnification were visualized per slide and 500cells/field were counted by an independent pathologist blindly. The sample was defined as positive if more than 10% of the nuclei of the tumour cells were dark brown as described in an earlier study[9].

Standard scale: Patients were defined as complete remission, or unconfirmed Complete Remission (CR), Partial Remission (PR), Stable Disease (SD) and Progressive Disease (PD) according to the international workshop to standardize response criteria for non-Hodgkin's lymphomas[10]. All patients in CR or PR were defined as effectively treated patients and all other patients were defined as ineffectively treated patients.

Clinical characteristics: Clinical characteristics, including age, gender, Ann Arbor staging, B symptoms, hemogram, myelogram, serum Lactate Dehydrogenase (LDH), imaging, previous treatments, international prognostic index (IPI), previous treatments cycles and lines of chemotherapy treatment, regimen and cycles of bortezomib-based combination chemotherapy were also extracted from electronic medical records which were collected from a computerized medical record system.

Statistical analyses: Mean values and Standard Deviations (SD) or median values and ranges were calculated for continuous variables whenever appropriate. For categorical variables, we calculated the counts and percentages. A t-test, nonparametric test, or chi-square test was used to compare the differences in characteristics and treatment efficacy between patients with an activated NF-κB signalling pathway and patients without. Crude and multivariable-adjusted logistic regression models were used to calculate the ORs for CR of p65 nuclear expression and efficiency for Relb nuclear expression. SPSS software (version 19.0) was used for all statistical analyses. A $p<0.05$ indicated results that were statistically significant.

RESULTS

The median age of the 48 patients, including 13 women and 35 men, was 47.5 years old (with an age range of 19-74 years). Based on the Ann Arbor staging classification, these patients were classified with stage I (n = 1), II (n = 5), III (n = 19) or IV (n = 23) NHL. Most of them were in the advanced stages (stages III-IV: 87.5%) and 11 patients had previously received two or more lines of CHOP or CHOP-based chemotherapy and 44 patients with poor initial responses or relapses. The median number of regimens of previous chemotherapy was 1 (with a range of 0-4) and the median number of cycles was 6 (with a range of 0-18). A total of 44 patients received 2-18 more cycles of bortezomib-based combination chemotherapy. Total 7 patients who were previously not treated with CHOP received bortezomib-based combination chemotherapy and among them, 4 accepted the preliminary treatment.

Tumour samples from each patient were examined for p65 and RelB protein expression. Total 18 samples taken from patients with DLBCL showed a positive expression of p65 only in the nuclei of cancer cells (37.5%) and 12 showed a positive expression of RelB (25%) (Table 1). Patients with positive p65 were more likely to be with a classification of III-IV tumour stage, without B symptoms, low levels of LDH and low levels of IPI (all $p<0.05$). Patients with positive RelB were more likely to be women, with lower BMI, high LDH and high levels of IPI (all $p<0.05$). Of all patients, 12 (25%) achieved CR, 13 (27.1%) reached PR, 8 (16.7%) stayed in an SD condition and 15 (31.2%) remained in a PD condition after bortezomib-based combination chemotherapy. Immunohistochemistry analyses revealed that all 18 tumours that exhibited p65-positive nuclear staining had a high level of treatment efficacy, while among the p65-negative patients there was 23.3% (7 out of the 30 patients) efficiency rate ($p<0.0001$). Among the 12 patients with RelB -positive nuclear staining, only 1 was in PR and 91.7% were inefficacy to the bortezomib-based combination chemotherapy, while among the RelB-negative patients the efficiency rate was 33.3% (12 out of the 36 patients) (P = 0.001) (Table 2). Compared with p65-negative nuclear staining, patients with p65-positive nuclear staining had a high CR rate for bortezomib-based combination chemotherapy (OR: 4.80; 95% CI: 1.173, 19.637), although it was not significant after adjusted for other potential confounders due to the limited sample size. Compared with RelB-negative nuclear staining, patients with RelB-positive nuclear staining had a low-efficiency rate for bortezomib-based combination chemotherapy (OR: 0.045,

Table 1: Characteristics of NHL patients with different p65 and RelB nuclear expression patterns

		P65, n (%)				RelB, n (%)		
Characteristics	Total	Nuclear positive (n = 18) (37.5%)	Nuclear negative (n = 30) (62.5%)	p-value	Total	Nuclear positive (n = 12) (25.0%)	Nuclear negative (n = 36) (75.0%)	p-value
Men	35 (72.9)	16 (88.9)	19 (63.3)	0.052	35 (72.9)	5 (41.7)	30 (83.3)	0.009
BMI (kg m^{2-1})	16.9±0.80	17.1±0.52	16.7±0.91	0.095	16.9±0.80	16.2±0.62	17.1±0.72	<0.0001
Age≤60	35 (72.9)	15 (83.3)	20 (66.7)	0.317	35 (72.9)	11 (91.7)	24 (66.7)	0.139
Stages				0.179				0.315
I-II	6 (12.5)	4 (22.2)	2 (6.7)		6 (12.5)	0 (0)	6 (16.7)	
III-IV	42 (87.5)	14 (77.8)	28 (93.3)		42 (87.5)	12 (100)	30 (83.3)	
B symptoms	28 (58.3)	5 (27.8)	23 (76.7)	0.002	28 (58.3)	8 (66.7)	20 (55.6)	0.737
LDH≥250 IU L^{-1}	19 (39.6)	3 (16.7)	16 (53.3)	0.016	19 (39.6)	8 (66.7)	11 (30.6)	0.041
IPI				0.037				0.042
1~2	22 (45.8)	12 (66.7)	10 (33.3)		22 (45.8)	2 (16.7)	20 (55.6)	
3~5	26 (54.2)	6 (33.3)	20 (66.7)		26 (54.2)	10 (83.3)	16 (44.4)	

IPI: International prognostic index, LDH: Lactate dehydrogenase, BMI: Body mass index

Table 2: Treatment efficacy in patients with different p65 and RelB nuclear expression patterns

	p65 nuclear staining, n (%)			RelB nuclear staining, n (%)		
Treatment efficacy	Positive (n = 18)	Negative (n = 30)	p-value	Positive (n = 12)	Negative (n = 36) (25.0%)	p-value
Prognosis						
Complete remission/unconfirmed	8 (44.4)	4 (13.3)	<0.0001	0 (0)	12 (33.3)	0.003
Partial remission	10 (55.6)	3 (10.0)		1 (8.3)	12 (33.3)	
Stable disease	0 (0)	8 (26.7)		4 (33.3)	4 (11.1)	
Progressive disease	0 (0)	15 (50.0)		7 (58.3)	8 (22.2)	
Efficacy						
Efficacy	18 (100)	7 (23.3)	<0.0001	1 (8.3)	24 (66.7)	0.001
Inefficacy	0 (0)	23 (76.7)		11 (91.7)	12 (33.3)	

Table 3: Calculated crude ORs and adjusted ORs for CR of P65 nuclear expression and efficiency for RelB nuclear expression

	P65*		Relb#	
Patients	Crude model OR (95% CI)	Adjusted model OR (95% CI)	Crude model OR (95% CI)	Adjusted model OR (95% CI)
Overall	4.80 (1.173, 19.637)	2.837 (0.311, 25.926)	0.045 (0.05, 0.395)	0.011 (0.0004, 0.319)
Non-GCB	14.0 (1.329, 147.4)	-	0.083 (0.008, 0.859)	1.024 (0.932, 1.125)
GCB	0.933 (0.078, 11.18)	0.029 (0.0001, 7.847)	-	-

*ORs are calculated for the CR, #ORs are calculated for the efficiency (CR and PR), GCB: Germinal centre-like B-cell

Table 4: Treatment efficacy in non-GCB and GCB patients with different p65 and RelB nuclear expression patterns

	p65 nuclear staining, n (%)			RelB nuclear staining, n (%)		
Treatment efficacy	Positive (n = 12)	Negative (n = 13)	p-value	Positive (n = 7)	Negative (n = 18)	p-value
Non-GCB						
Prognosis						
Complete remission/unconfirmed	7 (58.3)	1 (7.7)	<0.0001	0 (0)	8 (44.4)	0.006
Partial remission	5 (41.7)	1 (7.7)		1 (14.3)	5 (27.8)	
Stable disease	0	3 (23.1)		3 (42.9)	0 (0)	
Progressive disease	0	8 (61.5)		3 (42.9)	5 (27.8)	
Efficacy						
Efficacy	12 (100)	2 (15.4)	<0.0001	1 (14.3)	13 (72.2)	0.021
Inefficacy	0	11 (84.6)		6 (85.7)	5 (27.8)	
Treatment efficacy	Positive (n = 6)	Negative (n = 17)	p-value	Positive (n = 5)	Negative (n = 18)	p-value
GCB						
Prognosis						
Complete remission/unconfirmed	1 (16.7)	3 (17.6)	0.004	0 (0)	4 (22.2)	0.040
Partial remission	5 (83.3)	2 (11.8)		0 (0)	7 (38.9)	
Stable disease	0 (0)	5 (29.4)		1 (20.0)	4 (22.2)	
Progressive disease	0 (0)	7 (41.2)		4 (80.0)	3 (16.7)	
Efficacy						
Efficacy	6 (100)	5 (29.4)	0.005	0 (0)	11 (61.1)	0.037
Inefficacy	0 (0)	12 (70.6)		5 (100)	7 (38.9)	

95% CI: 0.05, 0.395) and it was still significant after adjusted for other potential confounders (OR: 0.011, 95% CI: 0.0004, 0.319) (Table 3).

A total of 25 cases of DLBCL were non-GCB DLBCL according to an immunohistochemistry measurement (Table 4). Out of 25 patients with non-GCB DLBCL, 7 (7 out of 12, 58.3%) with p65-positive nuclear staining and 0 (0 out of 7) with RelB-positive nuclear staining were in complete remission, while among those patients with p65-negative nuclear staining and with RelB-negative nuclear staining, only 1 (1 out of 13, 7.7%) and 8 (8 out of 18, 44.4%) experienced complete remission. In the GCB cases, 5 patients (29.4%) out of the 17 with p65-negative nuclear staining finally underwent effective treatment while the treatments of all 6 patients with a positive expression of p65 were effective ($p = 0.005$). For RelB nuclear staining, 38.9% of the patients (7 out of 18) with RelB-negative nuclear staining were effectively treated and 100% (5 out of 5) of the RelB-positive patients were effectively treated ($p = 0.037$). We further calculated the OR of CR for p65-positive was 14.0 (95% CI: 1.329, 147.4) and 0.083 (0.008, 0.859) of efficacy for RelB-positive among non-GCB patients (Table 3).

DISCUSSION

In this small cross-sectional study, we observed 48 patients with non-Hodgkin's lymphoma and found that the positive expression of p65 after nuclear staining and the negative expression of RelB after nuclear staining tended to indicate an effective treatment of bortezomib-based combination chemotherapy. However, due to the limited number of participants, further large scale, well-designed, prospective studies are warranted to confirm our findings.

We observed that 18 patients with DLBCL showed positive nuclear staining of p65 and 16 belonged to relapsed or refractory non-GCB cases. After treatment with two to six cycles of bortezomib-based combination chemotherapy, most of the patients with positive p65 showed efficacy to bortezomib-based combination chemotherapy: 7 patients achieved CR and 9 patients achieved PR. DLBCL could be classified into germinal centre-like DLBCL (GCB) and non-GCB groups according to the immunohistochemical expression of CD10, BCL6 and MUM1[11]. Furthermore, activated B-cell-like DLBCL (ABCDLBCL) could be picked out from non-GCB groups via the DNA microarray technique and gene expression

profiling[12], with the remaining part being unclassified DLBCL. Previous studies reported that the 5 year OS was significantly higher among those with GCB subtypes than those with non-GCB subtypes. The five year OS was 76% in cases with a GCB subtype, compared to only 34% in non-GCB cases[13]. Recently, evidence has accumulated that ABCDLBCL exhibits a constitutive activation of the NF-κB signalling pathway[4,14,15], which encouraged researchers to combine bortezomib with conventional chemotherapy to treat this subtype. Leonard[16] used bortezomib-based combination chemotherapy with R-CHOP as the initial treatment of 40 patients with DLBCL. The CR rate was 80% and the result also showed that non-GCB, which was associated with an inferior prognosis, had a similar effectiveness rate to GCB. Dunleavy[17] found similar results. Thus, bortezomib-based combination chemotherapy might be proven to be effective in the treatment of ABC DLBCL. Also, our study presented a similar phenomenon, 23 patients with relapsed or refractory non-GCB and received bortezomib-based combination chemotherapy with an ICE regimen, 4 patients achieved CR, in which 1 case was shown to express p65 and5 expressed p65 of 7 achieved PR.

We viewed that NF-κB activation in non-GCB DLBCL cases was slightly higher than in other types of DLBCL, especially for p65 (48% in non-GCB DLBCL and 26% in GCB DLBCL). There are several explanations for NF-κB activation in ABC DLBCL. ABC DLBCL often secretes B cell-activating factors from the tumour necrosis factor family, which then induce the activation of the NF-κB signalling pathway. This activation process requires the protein kinase C-associated kinase in DLBCL cells. Kim[18] showed that the suppression of protein kinase C-associated kinase expression inhibits NF-κB activity in ABC DLBCL cells, resulting in a significant increase in apoptosis. Another mechanism was associated with the CARD11 gene mutation[19,20].

Using gene spectrum analyses of 73 patients with relapsed or refractory mantle cell lymphoma in the phase 2 PINNACLE study Goy *et al.*[21] found an elevated p65 expression and a trend for a better response to chemotherapy, both of which were significantly associated with a longer overall survival period. Espinosa and colleagues[22] also showed that the activation of NF-κB by p65 was associated with a good prognosis by comparing the phosphorylation of p65, p50, p52 subunits and the expression of IκB in DLBCL. Martinez-Delgado[23] and Briones[24] confirmed the differences in the activation status of the NF-κB pathway between PTCL subgroups by using cDNA microarrays and an association with the low survival rate among patients with reduced expression of NF-κB genes. Our study found that the number of cases with p65-positive nuclear staining in the effective treatment group was significantly higher than that in the ineffective treatment group, which is consistent with the previous aforementioned studies[21-24]. One intriguing finding in our study was that the RelB-positive nuclear staining account for 33.3% of SD patients and 58.3% of PD patients but only one patient was PR and zero was CR. This result indicated the activation of the alternative pathway in the ineffective treatment group and a significant correlation was found between the activation of the alternative pathway and efficacy.

CONCLUSION

Our small cross-sectional study showed a significant difference in the activation of the NF-κB signalling pathway among various subtypes of NHL, which lead to different efficacy rates of bortezomib-based combination chemotherapy for patients of NHL. NF-κB activation through the canonical pathway, positive expression of p65 after nuclear staining and the negative expression of RelB after nuclear staining, is frequent in cases of NHL which demonstrate the satisfactory chemotherapeutical effects of bortezomib.

SIGNIFICANCE STATEMENT

Basic studies found that the Nuclear Factor-κB (NF-κB) signalling pathway can be activated inappropriately in NHL patients, suggesting that activation of the NF-κB signalling pathway is a key role in oncogenesis and the progression of lymphoid malignancies. However, limited evidence in human studies. This study discovers an effective treatment of bortezomib-based combination chemotherapy among patients with the positive of p65 and the negative of RelB. Our findings will help the physicians to provide precise treatment for patients with Non-Hodgkin's Lymphoma.

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