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ORIGINAL ARTICLE

Elevated SOX11 mRNA level correlates with favorable prognosis in mantle cell lymphoma

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Summary

Purpose: *To explore the prognostic value of SOX11 in patients with mantle cell lymphoma (MCL).*

Methods: *The clinical data and paraffin-embedded tissue of 75 primary MCL in Shanxi Tumor Hospital were collected, and the MCL international prognostic index (MIPI) was rechecked in all cases according to simplified (sMIPI) formula. The expression of SOX11 mRNA was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) and the relationship of survival with SOX11 mRNA and MIPI in MCL patients was evaluated.*

Results: *Median survival was 44 months in cases with low-risk, 31 months in cases with intermediate-risk and 30 months in cases with high-risk. There was statistically significant difference between low-risk and high-risk group (p=0.0033), while there was no statistical difference between low-risk group and intermediate-risk group (p=0.1067) and the intermediate-risk group and high-risk group (p=0.6149). Furthermore, cases were divided into group SOX11mRNA<M (median of SOX11 mRNA level) and group SOX11mRNA≥M in each MIPI group according to SOX11 mRNA expression, and the results of 3 groups all showed that median survival was shorter in group SOX11mRNA<M than that in SOX11mRNA≥M (p<0.05). Univariate analysis showed poorer survival was associated with blastoid transformation, ECOG≥2, p53 positive, bone marrow involvement, high-risk group and SOX11mRNA<M. Multivariate analysis showed blastoid transformation, high-risk group and SOX11mRNA<M were poor prognostic factors.*

Conclusions: *SOX11 mRNA level has certain prognostic value and SOX11 mRNA≥M was related to good prognosis.*

Key words: *mantle cell lymphoma, SOX11, prognosis*

Introduction

Mantle cell lymphoma (MCL) has a poorer prognosis compared with other B cell non-Hodgkin's lymphomas (NHL) [1,2]. MCL is a heterogeneous disease. Not all cases present aggressive course, with 10-15% having an indolent course [3,4]. So it is important to investigate more prognostic factors in MCL to provide a sound basis for determining the treatment strategy.

The MCL international prognostic index (MIPI) could predict the prognosis better than the IPI in MCL, although MIPI developed from IPI [5,6]. MIPI could clealy separate high-risk patients from the intermediate-risk and low-risk patients, however, it was difficult to tell the intermediate-risk and low-risk patients apart [5].

Recent research indicated that a gene that might have prognostic significance in MCL was SOX11. High expression of SOX11 was specific in MCL compared with other small B cell lymphomas that were easily confused with MCL, which resulted in considering SOX11 as one of the diagnostic markers [7]. As for the prognostic value, there

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were paradoxical conclusion [8-10]. Some studies have shown that high SOX11 expression was associated with good prognosis, but there were also some opposite conclusions [11,12]. In this study, we detected the mRNA level of SOX11 by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) in 75 MCL patients, analyzed the correlation between SOX11mRNA level combined with MIPI and median survival to assess the prognostic value of SOX11 in MCL.

Methods

Cases

The primary diagnostic paraffin-embedded tissues from 75 patients with MCL were collected between March 2005 and March 2014 in Shanxi Tumor Hospital. Meanwhile, 30 specimens with reactive lymphoid node were selected as controls. The detailed clinical data and survival information of all cases were retrospectively obtained from hospital records and by telephone follow-up. This study was approved by the Ethics Committee of Shanxi Tumor Hospital and in accordance with Helsinki Declaration. Informed consent was signed by all the study participants.

MIPI

The MIPI was rechecked in all cases according to simplified (sMIPI) formula [5]. All patients were stratified into low-risk, intermediate-risk and high-risk subgroup.

Immunohistochemistry (IHC)

Immunohistochemical methods were used to detect the expression of cyclin D1 and p53 in 75 patients with MCL. P53 was located in the nuclei, and was considered as positive when the number of positive cell was >10% [13,14].

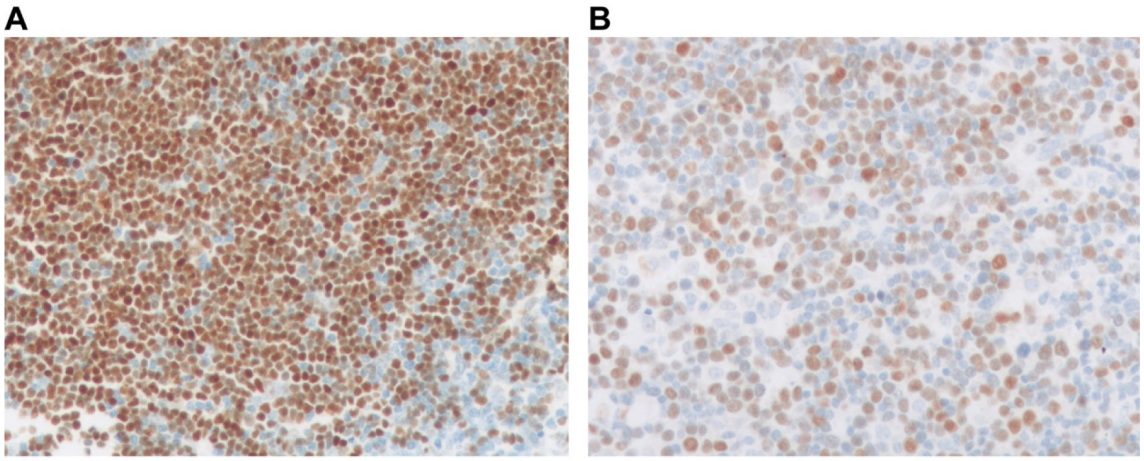

Figure 1. Immunohistological staining for detection of the expression of Cyclin D1 and p53 in patients with MCL. **A**: IHC Cyclin D1+ (x200); **B:** IHC p53+++ (x200).

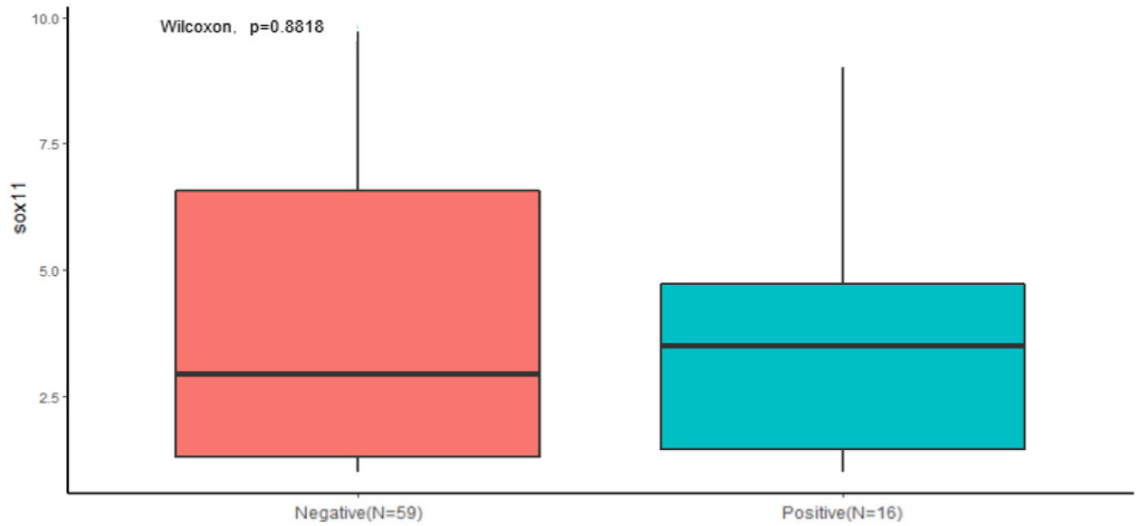

Figure 2. No significant difference in SOX11 mRNA expression between p53 positive and negative group.

RT-PCR

Total RNA was extracted from specimens using the Recover AII Total Nucleic Acid Isolation Kit (AM1975, ABI, Foster City, CA, USA). cDNA was synthesized and the product was amplified using 2-step RT-PCR kit (Qiagen, Nanjing, USA) according to the manufacturer's protocol, with specific primer for SOX11 (4331182, ABI, Foster City, CA, USA) and β-actin (4333762f, ABI, Foster City, CA, USA) as control. Conditions for amplification were 95°C for 30 s, 95°Cfor 5 s, 61°Cfor 30 s, 95°Cfor 15 s, 60°Cfor 60 s, 95°Cfor 15 s and 40 cycles. The expression level of SOX11 mRNA was analyzed by the $2^{-\Delta\Delta Ct}$ method.

Statistics

Analysis was performed with SPSS 22.0 software (IBM, Armonk, NY, USA). Measurement data presented skewness distribution, being described with median and interquartile range. Group comparisons in measurement data were conducted with Wilcoxon rank sum test, while multiple comparison with the Nemenyi method. Survival analysis was performed with Kaplan-Meier method and log-rank test was used to compare differences between groups. Univariate and multivariate analysis were performed with Cox proportional hazard regression model. P<0.05 was considered as statistically significant.

Results

Clinicopathologic characteristics

Among 75 cases of MCL, 58 were male (77%), 17 female (23%), and median age was 63 years (range 39-79). Forty-eight (64%) cases had ECOG 2-4, 56 (75%) cases had Ann Arbor stage III-IV. Twenty-one (28%), 31 (41%) and 23 (31%) cases had low-risk, intermediate–risk and high-risk according to MIPI, respectively. Positive 100% (75/75) of the cases were cyclin D1 positive, while 21% (16/75) were p53 positive (Figure 1A,1B).

Correlation between SOX11 mRNA expression and p53 gene variation

SOX11 mRNA expression was 3.742 in the p53 negative group, and 3.778 in the p53 positive group without statistical difference between the two groups (p=0.953) (Figure 2).

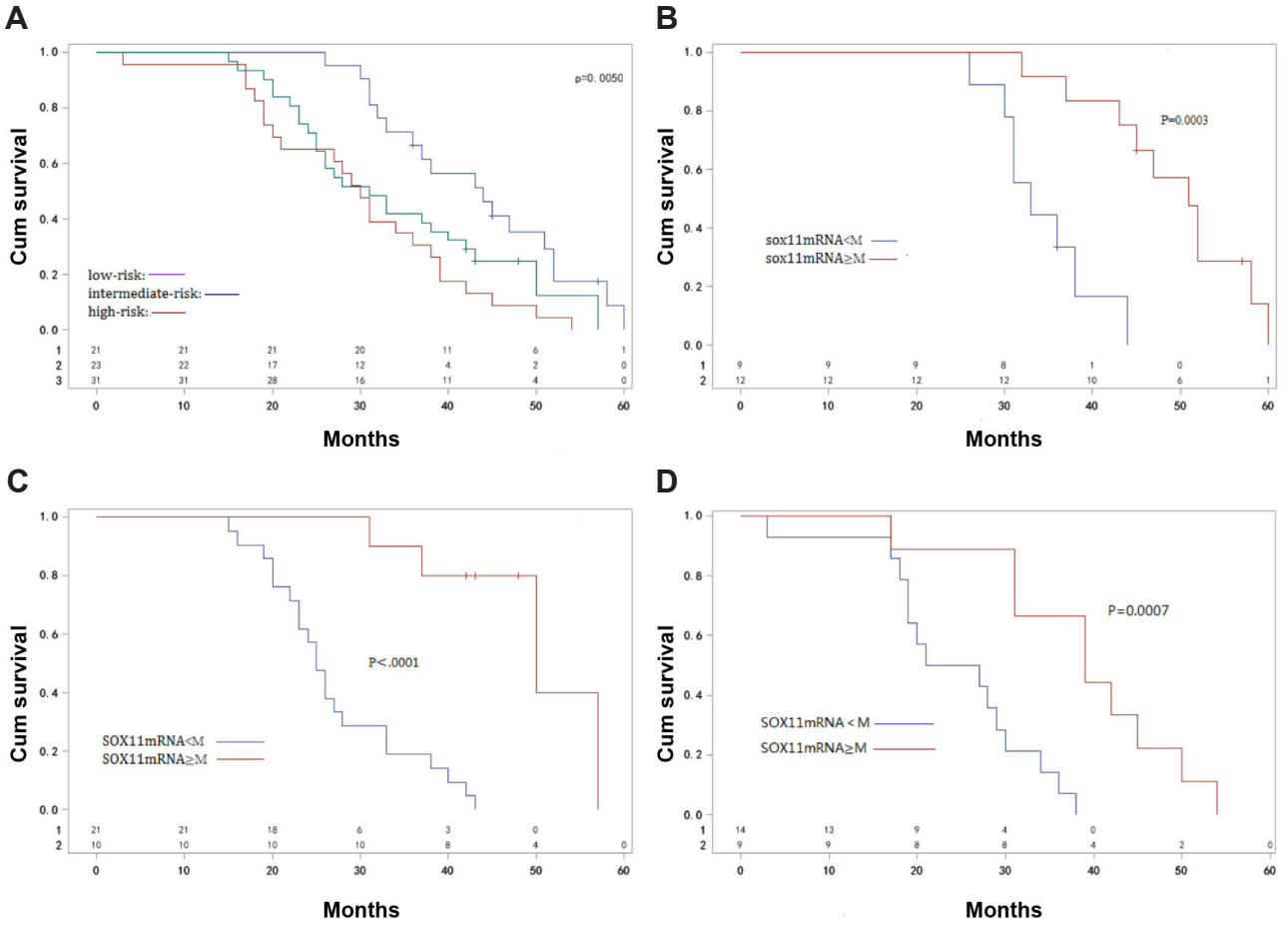

Figure 3. Survival analysis. **A:** Median survival was 44 months in low-risk group, 31 months in intermediate-risk group and 30 months in high-risk group, respectively. **B:** Median survival was shorter in SOX11 mRNA<M than that in SOX11 mRNA≥M in low-risk group. **C:** Median survival was shorter in SOX11 mRNA<M than that in SOX11 mRNA≥M in intermediate-risk group. **D:** Median survival was shorter in SOX11 mRNA<M than that in SOX11 mRNA≥M in high-risk group.

Survival analysis of MIPI

Median survival was 44 months in low-risk cases, 31 months in intermediate-risk cases and 30 months in high-risk cases, respectively. There was statistically significant difference between low-risk and high-risk group (p=0.0033), while there was no significant difference between low-risk group and intermediate-risk group (p=0.1067) and intermediate-risk group and high-risk group (p=0.6149) (Figure 3A).

Survival analysis of SOX11 mRNA in each MIPI group

Furthermore, cases were divided into SOX11 mRNA<M group and SOX11 mRNA≥M group in

Table 1. Univariate analysis of prognostic factor in MCL

Variables	*N*	*Median survival (months)*	*95%CI*	x^2	*p*
Age (years)				0.1004	0.7513
≥60	46	35	28-42		
<60	29	33	26-38		
Morphology				17.2585	<0.0001
Classic morphology	69	36	31-40		
Blastoid morphology	6	19.5	16-31		
KI67 (%)				0.012	0.9128
≥30	22	30.5	19-45		
<30	53	36	31-39		
ECOG PS				7.9864	0.0047
≥2	48	30	25-34		
<2	27	43	32-50		
WBC				1.7304	0.1884
≥10×10^9/L	11	34	15-39		
<10×10^9/L	64	33	30-40		
LDH (IU)				0.0691	0.7926
≥240	17	38	20-50		
<240	58	33	28-38		
β2-MG (mg/L)				2.59	0.1075
≥3	33	31	25-38		
<3	42	36.5	31-43		
p53				0.0118	0.9136
Positive	16	32.5	22-44		
Negative	59	33	29-38		
Ann Arbor Stage				1.2888	0.2563
I-II	19	33	23-47		
III-IV	56	33.5	30-38		
B symptoms				3.4043	0.065
No	62	34.5	30-42		
Yes	13	31	18-38		
Bone marrow MIPI					
Involvement	22	28	20-36	7.5177	0.0061
Normal	53	37	31-43		
Low-risk	21	44	33-52	10.5919	0.0050
Intermediate-risk	31	31	25-40		
High-risk	23	30	20-36		
SOX11 mRNA				8.2568	<0.0001
<M	44	27	23-31		
≥M	31	50	42-52		

p<0.05 shows statistical significance

Table 2. Multivariate analysis of prognostic factor in MCL

Variables	*β*	*SE*	*HR*	*95% CI*		*p*
				Lower limit	*Upper limit*	
Morphology						
Classic morphology *vs.* blastoid morphology	1.33315	0.507551	3.792973	1.40266	10.2567	0.008623472
MIPI						
Low-risk *vs.* high risk	0.916636	0.356894	2.500863	1.24251	5.0336	0.010217799
Low-risk *vs.* intermediate risk	0.54299	0.323706	1.721146	0.91269	3.2461	0.093460963
SOX mRNA						
<M *vs.* ≥M	-2.16778	0.367616	0.114431	0.05567	0.2352	<0.0001

p<0.05 shows statistical significance

each MIPI group according to SOX11 mRNA expression, and the results of 3 groups all showed median survival was shorter in group SOX11 mRNA<M than that in SOX11 mRNA≥M (p<0.05) (Figure 3B, C, D).

Univariate analysis and multivariate analysis of prognostic factors

At alpha=0.05 level, univariate analysis showed poorer survival was associated with blastoid transformation, ECOG ≥2, p53 positive, bone marrow involvement, high-risk group and SOX11 mRNA<M. Multivariate analysis showed blastoid transformation, high-risk group and SOX11 mRNA<M were independent poor prognostic factors (Tables 1 and 2).

Discussion

In addition to its diagnostic value against MCL [10,15], several publications have also suggested that SOX11 may be associated with clinical outcomes [2,7,11]. Wang et al. [16] studied 53 MCL cases and found that the median survival of 5 cases with negative SOX11 expression in the nuclei was significantly shorter than those with positive nuclear SOX11 expression (494 days and 1488 days, respectively). In contrast, Fernandez et al. [17] and Navarro et al. [18] reported opposite conclusion that median survival of patients with positive SOX11 expression was shorter than that of patients with negative SOX11 expression. Also, in these studies [3, 19], a specific subtype of MCL was reported characterized with non-nodal, leukemic presentation, mutated IGVH, negative SOX11 expression and indolent clinical disease course. Based on these results, lack of SOX11 expression was gradually regarded as a feature of indolent MCL. However, Nygren et al. [12] analyzed 186 MCL patients in a population-based cohort and showed SOX11 negative cases (13/173) had shorter median overall survival compared with SOX11 positive cases (160/173). Of note, in this study the fraction of positive SOX11 cases was 88% among indolent cases, which was not significantly different compared with 93% among nonindolent cases. Thus, identifying indolent MCL should combine clinical presentation with the status of IGVH mutation and SOX11 expression. Moreover, in this report the fraction of p53 strongly positive cases in SOX11- cases was statistically increased compared to SOX11+ cases (69 vs 16%, p<0.001), as it is that known p53 positive expression is a unfavorable prognostic factor in malignant neoplasms [20-23],which might contribute to the poorer survival in SOX11- cases. Nordström et al. [11] analyzed 127 MCL cases from the combined MCL2 (n=58) and MCL3 (n=69) trials that also investigated cases with SOX11 low expression (negative, weak and intermediate expression by ICH). The authors reported significantly shorter median survival than those with SOX11 high expression (strong expression by ICH) (p=0.022). In the study, strong p53 expression using IHC was found in 29% (10/35) of SOX11 negative cases, which was significantly different compared with SOX11 positive cases in which no strong p53 case was detected. This might be one of the factors that SOX11 negative cases had short survival. In our study, patients with SOX11 mRNA<M had shorter median overall survival than those with SOX11 mRNA≥M, either for all group patients or for each IPI subgroup. Neither univariate analysis nor multivariate analysis of prognostic factors showed SOX11 mRNA≥M was a good prognostic factor. There was no statistical correlation between SOX11 mRNA expression and p53 expression.

The prognostic value of SOX11 has been still unconfirmed and several factors might contribute to this controversial conclusion [13,24-26]: 1) the cut off value of SOX11 positive was not unified; 2)

the fraction of indolent MCL in different cohort studies was different; 3) the different frequencies of p53 strong expression might be one of the reasons. It might be better to separate classical MCL from indolent MCL when evaluating SOX11 prognostic value. Correlation between lack of SOX11 expression and p53 positive expression is unclear and more studies are needed to explore this issue.

Conclusions

There are some complex mechanisms for SOX11 prognostic significance in MCL, resulting to conflicting conclusions, however published reports still have shown its potential value. Moreover, due to its high expression in MCL cases, SOX11 might become a therapeutic target for MCL in the future.

Acknowledgements

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Conflict of interests

The authors declare no conflict of interests.

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