Prognostic significance of serum B-lymphocyte stimulator level in Hodgkin's lymphoma

B-lymphocyte stimulator (BLyS) plays a critical role in the survival of B-lymphocytes. In 50 patients with Hodgkin's lymphoma BLyS levels were higher in newly diagnosed patients (median 2.0 ng/mL, range <0.3–56.0) and relapsed patients (8.7 ng/mL, range 1.5-71.5) than in 93 healthy donors (<0.3 ng/mL, range <0.3–0.5). High serum BLyS levels (≥2.0 ng/mL) in newly diagnosed patients were associated with resistance to therapy (p=0.01) and shorter progression-free survival (log-rank p=0.029, 2-year rate 64% vs 100%). Serum BLyS levels may have prognostic significance in Hodgkin's lymphoma.

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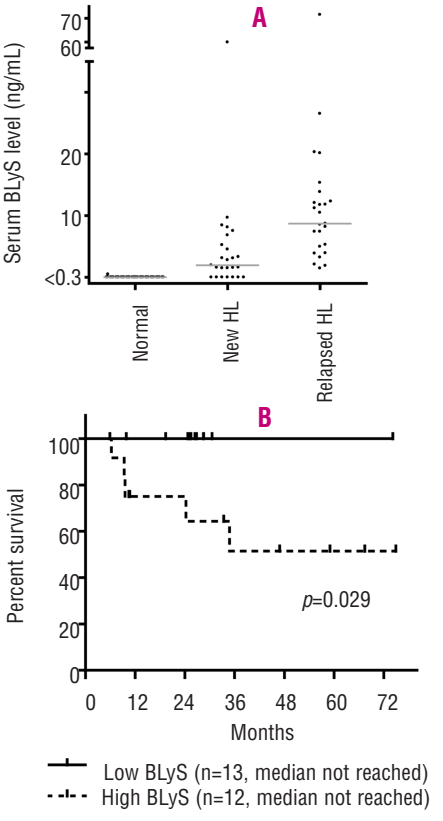
B-lymphocyte stimulator (BLyS), a transmembrane protein that belongs to the tumor necrosis factor superfamily, is an important survival factor for both benign and malignant B-lymphocytes.[1-3] It is normally expressed by macrophages, monocytes, and dendritic cells, but not by benign B or T cells.[1] Aberrant BLyS expression has been observed in a variety of lymphoid malignancies,[4-6] and the elevated serum levels of BLyS in patients with non-Hodgkin's lymphoma (NHL) may carry a prognostic value.[7] Recent *in vitro* experiments demonstrated that BLyS was also expressed by Reed-Sternberg cells of Hodgkin's lymphoma (HL) as well as the reactive infiltrate of HL, such as macrophages, granulocytes and plasma cells, serving as an important survival factor for malignant cells.[8] Here we examined the serum levels of BLyS in patients with HL, and evaluated their prognostic value.

Serum samples were obtained from 93 healthy volunteers and 50 patients with HL (25 at initial diagnosis and 25 at relapse). The patients' samples were deposited in the M. D. Anderson Cancer Center Lymphoma Serum Bank. All patients and volunteers gave consent to blood donation in accordance with the Institutional Review Board guidelines. Serum levels of BLyS were measured by enzyme-linked immunosorbent assay (ELISA) using a monoclonal murine antibody as the capture reagent and a goat polyclonal antibody as the detector.[9] The lower limit of detection of the assay is 0.3 ng/mL. Serum BLyS levels were correlated with responses to initial therapy, progression-free survival (PFS), and overall survival (OS). PFS was calculated from the date of blood drawing (either at initial diagnosis or relapse) to the date of observed disease progression or death. Fisher's exact test and the Mann-Whitney test were used for comparisons of categorical and continuous data, respectively. Survival curves were estimated according to the Kaplan-Meier method, and the two groups were compared by the log-rank test.

The levels of BLyS in healthy individuals ranged from <0.3 to 0.5 ng/mL, with a median value of <0.3 ng/mL (Figure 1A). Serum BLyS levels were elevated in patients with newly diagnosed HL (median 2.0 ng/mL, range <0.3–56.0, p<0.0001) and were even higher in relapsed patients (median 8.7 ng/mL, range 1.5–71.5, p<0.0001). In newly diagnosed patients, a high BLyS level (≥2.0 ng/mL) was associated with other unfavorable characteristics including male sex (p=0.02), stage 4 disease (p=0.07), bulky disease ≥7.5cm (p=0.03), high lactate dehydrogenase (LDH) (p<0.01), high β2 microglobulin (p=0.01), and a less than complete response to treatment (p=0.01) (Table 1).



Numbers evaluated	93	25	25
Median follow-up duration	–	53.3	80.2
Lowest quartile	<0.3	<0.3	1.5
First quartile value	<0.3	<0.3	5.0
Median value	<0.3	2.0	8.7
Third quartile value	<0.3	5.3	12.3
Highest quartile	0.5	56.0	71.5
Mean value	<0.3	5.3	12.2
Values above detectable level	1%	72%	100%
Values ≥ 2 ng/mL (%)	0%	48%	92%

Figure 1. A. Serum BLyS levels in normal individuals and patients with lymphoma. Data are shown according to prior treatment status and histology. The horizontal line represents the median value for each subgroup. B. Progression-free survival in patients with newly diagnosed HL according to serum BLyS levels. The median value of 2.0 ng/mL was used to distinguish the two groups.

All newly diagnosed patients with HL were treated with three to six cycles of ABVD chemotherapy with or without radiation therapy. The median follow-up duration was 53.3 months (range 9.6–80.2). Patients with serum BLyS levels ≥2.0 ng/mL had a shorter PFS than those with BLyS levels <2.0 ng/mL, with 2-year PFS rates of 64% and 100%, respectively (log-rank p=0.029, Figure 1B). The same trend was observed by analysis using the third quartile value (5.3 ng/mL) as a cut off, but the differences were not statistically significant (p=0.19). By univariate analyses (separate log-rank tests) for PFS in patients with newly diagnosed HL among seven known unfavorable prognostic factors[10] [age >45 years, male sex, stage 4 disease, WBC ≥1.5×10^9/L, lymphocyte count <0.6×10^9/L, albumin <4.0 mg/dL, hemoglobin <10.5 g/dL) in addition to high BLyS level, LDH >normal limit and presence of bulky disease (≥7.5 cm], only high BLyS level was significantly associated with shorter PFS (p=0.029, hazard ratio 6.65 [95% confidence interval 1.06-

Table 1. Prognostic significance of an elevated serum BLyS level in patients with newly diagnosed Hodgkin's lymphoma.

	Total (N)	*High BLyS (N, %)*	*p value*
Total	25	12 (48%)	
Age			
≥45 years	20	10 (50%)	
>45 years	5	2 (40%)	0.69
Sex			
Female	14	4 (29%)	
Male	11	8 (73%)	0.02
Stage			
Stage 1	1	0 (0%)	
Stage 2	8	2 (25%)	
Stage 3	6	3 (50%)	4 vs other
Stage 4	10	7 (70%)	p=0.07
Bulky disease (≥7.5cm)			
No	19	7 (37%)	
Yes	6	5 (83%)	0.03
Lactate dehydrogenase			
Normal	17	5 (29%)	
High	8	7 (88%)	<0.01
β2 microglobulin			
Low (<3 mg/L)	21	8 (38%)	
High (≥3 mg/L)	4	4 (100%)	0.01
Hemoglobin			
Low (<10.5 g/dL)	3	2 (67%)	
Normal (≥10.5 g/dL)	22	10 (45%)	0.38
Albumin			
Low (<4.0 mg/dL)	10	6 (60%)	
High (≥4.0 mg/dL)	15	6 (40%)	0.32
White blood cell count			
Normal (< 1.5×10^9/L)	22	10 (45%)	
High (≥1.5×10^9/L)	3	2 (67%)	0.49
Lymphocyte count			
Normal (≥0.6×10^9/L)	22	10 (45%)	
Low (<0.6×10^9/L)	3	2 (67%)	0.49
Sum of seven factors*			
0-2	18	6 (33%)	
3-5	7	6 (86%)	0.02
Response			
CR	22	9 (41%)	
Not CR	3	3 (100%)	0.01

*CR indicates complete response; *seven factors: age >45 years, male sex, stage 4 disease, WBC ≥1.5×10^9/L, lymphocyte count <0.6×10^9/L, albumin <4.0 mg/dL, hemoglobin <10.5 g/dL.*

41.7]). Next, since BLyS levels were associated with advanced stage disease, the analysis was restricted to 17 patients with advanced stage HL (stage 2 with bulky disease, stage 3, and stage 4). The same trend in the survival difference by BLyS levels was still observed in this analysis, although statistically not significant (p=0.19). Among all patients with newly diagnosed HL, 5-year OS rates were 100% and 83% for those with low BLyS and high BLyS levels, respectively (log-rank p=0.27).

In summary, we show for the first time that patients with HL have elevated levels of serum BLyS, and that a high BLyS level is associated with several other poor prognostic characteristics. Together with the recent *in vitro* studies showing the role of BLyS in survival of HL cells,[8] our data suggest that BLyS plays a significant role in patients with HL. Whether the prognostic significance of a high BLyS level is independent of other known prognostic factors is yet to be determined in larger scale studies. Nonetheless, a high serum BLyS level was found to be the best prognostic marker by univariate analyses, suggesting that it does have a strong prognostic value in HL.

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