The prognostic significance of β2-microglobulin in patients with Hodgkin's lymphoma

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Background and Objectives. Serum β2-microglobulin
(sβ2m) is an established prognostic factor for multiple
myeloma and non-Hodgkin's lymphoma, but only limited
data suggest an adverse prognostic significance for Hodgk-
in's lymphoma (HL). This study was undertaken to exam-
ine the impact of sβ2m on the prognosis of patients with
HL.

Design and Methods. sβ2m was measured by a radioim-
munoassay (upper normal limit 2.4 mg/L), in pretreatment
serum samples of 232 patients with HL, who were then
treated with ABVD or equivalent regimens with or without
radiotherapy. Multivariate survival analysis was based on
Cox's proportional hazards model.

Results. Main patients' characteristics: median age 30.5
years (14-78); 58% males; 68% nodular sclerosis, 20%
mixed cellularity and 12% lymphocyte predominance; 34%
B-symptoms; 24% Ann Arbor stage I, 49% II, 18% III and
9% IV. Elevated sβ2m levels were detected in 65/232
patients (28%) and correlated with older age ($p<0.001$),
mixed cellularity ($p=0.03$), B-symptoms ($p=0.002$),
advanced stage ($p=0.02$), ≥5 involved sites ($p=0.02$),
inguinal/iliac involvement ($p=0.009$), lymphocytopenia
($p=0.002$) and elevated lactate dehydrogenase ($p=0.01$).
The 7-year failure free survival (FFS) was 75% vs. 72% for
patients with normal vs. elevated sβ2m ($p=0.15$). The cor-
responding 7-year overall survival (OS) rates were 86% vs.
52% ($p=0.003$). In multivariate analysis, elevated sβ2m
was not predictive of FFS, but was independently associ-
ated with inferior OS ($p=0.01$), along with the number of
involved sites ($p<0.001$).

Interpretation and Conclusions. sβ2m is not a potent prog-
nostic factor for FFS in optimally treated patients with HL.
However sβ2m may be predictive of OS, probably due to
its effect on the timing of treatment failure.
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Key words: Hodgkin's lymphoma, β2-microglobulin,
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Although Hodgkin's lymphoma (HL) is usually
a curable disease, 5-10% of early and 20-
40% of advanced stage patients either
progress during first-line therapy or relapse fol-
lowing an initial remission achieved by chemo-
therapy (CT) or combined modality therapy.[1-12]
ABVD[13] is considered as a standard CT regimen,
either alone or in combination with MOPP in alter-
nating[14] or hybrid schedules.[7] These regimens
appear to be equivalent.[7-9]

In the effort to identify patients who have a high
probability of failing to benefit from standard
treatment, several groups have reported prognos-
tic models incorporating clinical and routine labo-
ratory parameters.[10,15-20] However, the reproducible
identification of sizeable subgroups of patients
with failure-free survival (FFS) <50%, who might
be candidates for aggressive first-line treatment,
has not been achieved. In order to reach this goal,
two approaches have been followed. The first is the
combination of various prognostic models, which
may be more efficient than each model separate-
ly.[20] The second is the identification of biological
factors, such as cytokines, cytokine receptors,
adhesion molecules and molecular markers, which
are promising in providing new independent and
biologically sensible prognostic factors.[21-31]

β2-microglobulin is the light chain molecule of
the histocompatibility complex class I antigen,
found at the membrane of almost all nucleated
cells.[32] The main source of β2-microglobulin in the
serum and other body fluids is membrane turnover.
Serum β2-microglobulin levels are elevated in a
considerable number of patients with multiple
myeloma, non-Hodgkin's lymphomas, and B-
chronic lymphocytic leukemia, and have been
shown to be an independent prognostic factor for
these diseases.[33-36]

The reported series regarding the prognostic sig-
nificance of β2-microglobulin in HL have reached
contradictory conclusions, usually analyzing rela-
tively small populations of patients,[30,37,38] treated

with heterogeneous strategies, which were usually inferior to current standard therapy.[30,37-39] Based on these considerations, we evaluated the frequency of elevated serum β_2-microglobulin, its association with other presenting clinical and laboratory features and its prognostic implication in a series of 232 patients with HL, treated homogeneously with ABVD or equivalent regimens with or without radiotherapy (RT) in our Unit.

Design and Methods

Patients

Patients with HL were included in this study if they were older than 14 years, were HIV-negative, had pretreatment serum β_2-microglobulin levels available, and had received treatment with anthracycline-based CT with or without RT. Serum samples for β_2-microglobulin determination were collected between 1988 and 2001. During this period, 521 patients with HL received their primary treatment in the Hematology Section, Day Care Clinic of the Laikon General Hospital at the National and Kapodistrian University of Athens, Greece. Of these, 497 were treated with ABVD or equivalent regimens. Based on the inclusion criteria, 232 patients with HL formed the basis of the present study. Their characteristics were compared with those of the 265 patients who had also received anthracycline-based chemotherapy with or without radiotherapy during the same period, but for whom pretreatment serum β_2-microglobulin levels were not available.

Staging and routine laboratory evaluation

All patients were clinically staged according to the Ann Arbor system,[40] using standard staging procedures. The number of involved anatomic sites was determined as described elsewhere.[11] Hemoglobin, white blood cell counts and differential, erythrocyte sedimentation rate (ESR), serum albumin and serum lactate dehydrogenase (LDH) levels were measured by standard assays. Anemia was defined as the presence of hemoglobin levels < 13 g/dL for males and <11.5 g/dL for females. Serum albumin was analyzed at a cut-off of 3.5 g/dL, which was the lower normal limit in our laboratory. The International Prognostic Score (IPS) was determined as previously described.[10]

Serum β_2-microglobulin determination

Serum β_2-microglobulin was measured by a radioimmunoassay (Pharmacia) in serum samples which had been drawn prior to treatment initiation and had been stored at –70°C. The range of normal values was 1.0-2.4 mg/L.

Therapy

Early Ann Arbor stage (AAS IA,IIA) and most AAS IIIA patients received ABVD or EBVD plus low dose, involved field RT[2] (n=150). AAS IB, IIB, IIIB and IV as well as one AAS IIIA patient were treated with alternating MOPP/ABVD[14] (n=12), the MOPP/ABV hybrid regimen[7] (n=12), or ABVD (n=58), usually without RT. All these regimens are currently considered equivalent.[1,7-9]

Statistical analysis

The distribution of the clinical and laboratory characteristics among patients with known and unknown serum β_2-microglobulin levels and the frequency of elevated serum β_2-microglobulin levels among various subgroups of patients defined by other known prognostic factors were compared by the χ^2 test.[41]

Failure-free survival (FFS) was defined as the time interval between treatment initiation and treatment failure or last follow-up. Failure was defined as inability to achieve complete or partial remission (CR, PR) during initial therapy, requiring a switch to another CT regimen, or progression after an initial complete or partial remission. Patients with toxic death during primary treatment and death in first remission, even if presumably attributed to long-term effects of treatment, were censored at the time of death. Overall survival was defined as the time interval between treatment initiation and death from any cause or last follow-up. Hodgkin's lymphoma specific survival was defined as the time interval between treatment initiation and death from progressive HL or last follow-up. Survival after failure was defined as the time interval between the documentation of treatment failure (primary failure or relapse) and death from any cause or last follow-up. The estimation of actuarial FFS or survival was performed by the method of Kaplan-Meier.[42] The identification of prognostic factors in univariate analysis was based on the log-rank test.[43] The identification of independent prognostic factors was performed using Cox's proportional hazards model.[44] A forward stepwise selection procedure, with entry and removal criteria of p=0.05 and p=0.10, respectively, was used. For multivariate analysis of survival after failure, these criteria were modified to p=0.10 and p=0.15, respectively, because of the low number of patients.

Results

Patients' characteristics

The distribution of baseline clinical and laboratory characteristics was not significantly different

Table 1. Comparison of presenting clinical and laboratory features between patients with known and unknown serum β$_2$-microglobulin levels.

Clinical or laboratory feature studied	Serum β$_2$-microglobulin Levels			
	Known (n=232)		Unknown (n=265)	p
	#	%	#	%
Age median (range)	30.5 (14-78)		30.0 (13-82)	0.92
≥45 years	58/232	25	63/265	24	0.75
Sex (male)	134/232	58	132/265	50	0.08
Histology					0.14
Nodular sclerosis	158/225	68	172/258	67	
Mixed cellularity	41/225	20	63/258	24	
Lymphocyte predominance	26/225	12	21/258	8	
Lymphocyte depletion	0	0	2/258	1	
Unclassified/unknown	7	–	7	–	
B-symptoms	79/232	34	92/265	35	0.88
Ann Arbor clinical stage					0.08
I	55/232	24	62/265	23	
II	114/232	49	127/265	48	
III	42/232	18	34/265	13	
IV	21/232	9	42/265	16	
Involved anatomic sites (≥5)	31/232	13	41/265	16	0.51
Inguinal and/or iliac involvement	47/230	20	49/263	19	0.61
Anemia	80/230	35	95/255	37	0.57
Leukocytosis (≥15×10⁹/L)	28/228	12	46/255	18	0.08
Lymphocytopenia (<1.0×10⁹/L)	28/208	14	22/206	11	0.39
ESR (≥ 50 mm 1st hour)	79/186	43	97/206	47	0.36
Serum albumin <3.5 g/dL	19/212	9	50/161	31	<0.001
LDH levels elevated	60/188	32	50/170	29	0.61
International Prognostic Score ≥3	41/215	19	54/211	26	0.11

Table 2. Correlation of serum β$_2$-microglobulin levels with other known prognostic factors in 232 patients with Hodgkin's lymphoma.

Clinical or laboratory factor	Serum β$_2$-microglobulin >2.4 mg/L (%)	p
Age (<45 vs ≥45 years)	19 vs 55	<0.001
Sex (male vs female)	30 vs 26	0.47
Histology (NS vs MC vs LP)¶	24 vs 44 vs 19	0.03
B-symptoms (no vs yes)	22 vs 41	0.002
Ann Arbor clinical stage		
I vs II vs III vs IV	15 vs 27 vs 41 vs 43	0.02
I/II/III vs IV	27 vs 43	0.11
Involved anatomic sites (≤4 vs ≥5)	25 vs 45	0.02
Inguinal/iliac involvement (no vs yes)	24 vs 43	0.009
Anemia (no vs yes)	23 vs 36	0.03
White blood cells (< vs ≥15×10⁹/L)	27 vs 39	0.16
Lymphocytopenia (≥ vs <1.0×10⁹/L)	26 vs 54	0.002
ESR (< vs ≥50 mm the 1st hour)	21 vs 30	0.13
Serum albumin (≥3.5 vs < 3.5 g/dL)	25 vs 42	0.12
LDH levels (normal vs elevated)	23 vs 40	0.01
International Prognostic Score (<3 vs ≥3)	21 vs 54	<0.001

NS=nodular sclerosis; MC=mixed cellularity; LP=lymphocyte predominance.

between the 232 patients with known and the 265 patients with unknown serum β$_2$-microglobulin levels with the exception of the higher frequency of hypoalbuminemia in the group with unknown levels (Table 1). The median follow-up of currently alive patients with known β$_2$-microglobulin levels was 29 months.

Serum β$_2$-microglobulin Levels

Elevated β$_2$-microglobulin levels were found in 65/232 patients (28%).

The correlation between serum β$_2$-microglobulin levels and other known prognostic factors is shown in Table 2. Serum β$_2$-microglobulin levels were elevated in 43% of patients with AAS IV disease, 41% of those with AAS III, 27% with AAS II and 15% with AAS I (p=0.02). We also observed significant associations between serum β$_2$-microglobulin levels and advanced age (p<0.001), B-symptoms (p=0.002), number of involved anatomic sites (p=0.02), inguinal/iliac involvement (p=0.009), mixed cellularity subtype (p=0.03), anemia (p=0.03),

lymphocytopenia (p=0.002), elevated LDH levels (p=0.01) and high IPS (p<0.001).

Univariate survival analysis

Failure-free survival. The 7-year FFS was 74% for the 232 patients with known serum β$_2$-microglobulin levels and 80% for the 265 patients with unknown levels (p=0.67). We observed a trend towards a lower FFS for patients with elevated serum β$_2$-microglobulin levels. At 7 years, FFS was 75% vs 72% for patients with normal and elevated serum β$_2$-microglobulin levels, respectively (p=0.15, Figure 1). Among patients with low IPS (<3), the 7-year FFS for those with normal and elevated serum β$_2$-microglobulin levels was similar [76% and 86%, respectively (p=0.74)]. The corresponding figures among patients with high IPS (≥3) were 65% and 44% (p=0.52). Significant predictors of inferior FFS were AAS IV (p=0.0001), B-symptoms (p=0.003), involvement of ≥5 anatomic sites (p<0.0001), inguinal/iliac involvement (p=0.007), ESR ≥50 (p=0.003) and IPS ≥3 (p=0.0002) as shown in Table 3.

Overall survival. The 7-year overall survival (OS) was 82% vs 89% for patients with known and unknown serum β$_2$-microglobulin levels, respectively (p=0.40). Elevated serum β$_2$-microglobulin level was predictive of OS, since OS at 7 years was
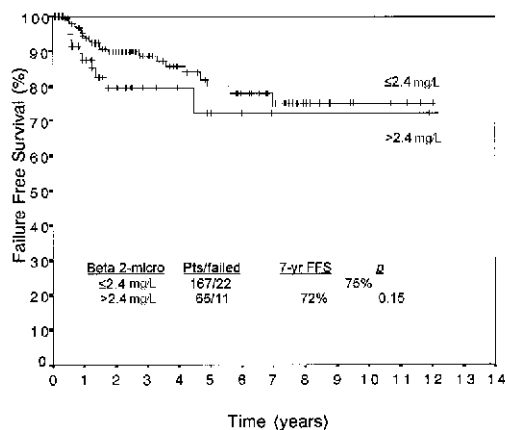
Figure 1. Effect of serum β$_2$-microglobulin levels on failure-free survival of 232 patients with Hodgkin's lymphoma, treated with ABVD or equivalent regimens, with or without radiation therapy.
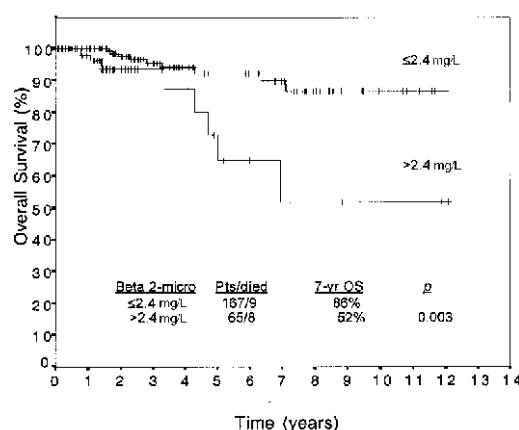

Figure 2. Effect of serum β$_2$-microglobulin levels on overall survival of 232 patients with Hodgkin's lymphoma, treated with ABVD or equivalent regimens, with or without radiation therapy.

Table 3. Univariate analysis of prognostic factors in 232 patients with Hodgkin's lymphoma.

Prognostic factor	7-year FFS (%)	p	7-year OS (%)	p
Serum β$_2$-microglobulin (≤ vs >2.4 mg/L)	75 vs 72	0.15	86 vs 52	0.003
Age (<45 vs ≥45 years)	81 vs 53	0.24	90 vs 52	0.03
Sex (male vs female)	68 vs 77	0.74	80 vs 86	0.81
Histology (NS vs MC vs LP)§	76 vs 68 vs 61	0.74	82 vs 73 vs 84	0.94
B-symptoms (no vs yes)	79 vs 62	0.003	85 vs 76	0.22
Ann Arbor stage I vs II vs III vs IV	81 vs 78 vs 72 vs 44	0.0006	100 vs 86 vs 45 vs 68	0.003
I/II/III vs IV	77 vs 44	0.0001	83 vs 68	0.02
Involved anatomic sites (≤4 vs ≥5)	78 vs 48	<0.0001	90 vs 39	<0.0001
Inguinal and/or iliac involvement (no vs yes)	79 vs 49	0.007	86 vs 58	0.006
Anemia (no vs yes)	75 vs 71	0.07	87 vs 69	0.04
White blood cells (< vs ≥15×10^9/L)	73 vs 79	0.25	80 vs 96	0.72
Lymphocytopenia (≥vs <1.0×10^9/L)	74 vs 69	0.10	82 vs 29	0.03
ESR (< vs ≥50 the 1st hour)	76 vs 60	0.003	90 vs 76	0.21
Serum albumin (≥ vs < 3.5 g/dL)	77 vs 60	0.27	85 vs 60	0.16
LDH levels (normal vs elevated)	80 vs 78	0.10	96 vs 58	0.07
International Prognostic Score (<3 vs ≥3)	77 vs 53	0.0002	82 vs 48	0.004

§NS = nodular sclerosis; MC = mixed cellularity; LP = lymphocyte predominance; FFS = failure-free survival; OS = overall survival.

86% versus 52% in patients with normal and elevated serum β$_2$-microglobulin levels, respectively (p=0.003, Figure 2). Among patients with low IPS (<3), the 7-year OS for those with normal and elevated serum β$_2$-microglobulin was 92% and 45% (p=0.1). The corresponding figures among patients with high IPS (≥3) were 56% and 50% (p=0.36).

Other significant predictors of overall survival in univariate analysis were AAS IV (p=0.02), involvement of ≥5 anatomic sites (p<0.0001), inguinal/iliac involvement (p=0.006), age ≥45 years (p=0.03),

anemia (p=0.04), lymphocytopenia (p=0.03) and IPS ≥3 (p=0.004) as shown in Table 3.

Multivariate survival analysis

Independent prognostic factors for FFS were AAS IV (p=0.02) and involvement of ≥ 5 anatomic sites (p=0.02) (Table 4). Serum β$_2$-microglobulin levels had no independent effect on FFS. In contrast, serum β$_2$-microglobulin level was a powerful independent prognostic factor for overall survival (p=0.01), along with the number of involved anatomic sites (p<0.001), as indicated in Table 4.

Table 4. Multivariate analysis of prognostic factors for failure-free and overall survival in 232 patients with Hodgkin's lymphoma.

Prognostic Factor	Exp(b)	Relative risk 95% CI	p
Failure-free survival			
Ann Arbor clinical stage (IV vs I/II/III)	3.0	1.2-7.6	0.02
Involved anatomic sites (≥5 vs ≤4)	2.9	1.2-6.6	0.02
Overall survival			
Serum β₂-microglobulin (> vs ≤2.4 mg/L)	3.5	1.3-9.4	0.01
Involved anatomic sites (≥5 vs ≤4)	5.7	2.2-15.0	<0.001

Abbreviations: exp(b)=relative risk; 95% CI= 95% confidence intervals.

Causes of death and survival after failure

So far, 17 deaths have been recorded. Among them 16 (94%) were related to HL, with 13 being directly related to progressive HL and 3 attributable to the applied treatment (two cases of secondary non-Hodgkin's lymphomas and one of congestive heart failure in first complete remission). Multivariate analysis of prognostic factors for Hodgkin's lymphoma-specific survival provided similar results with overall survival analysis (data not shown).

Patients with initially elevated serum β₂-microglobulin levels tended to have an inferior survival after treatment failure, as compared to those with normal levels, although both groups were treated with similar salvage therapy. At 4 years post-failure, 41% of patients with normal serum β₂-microglobulin levels were alive, as compared to 0% of those with elevated levels (p=0.06). In contrast advanced age did not correlate with inferior survival after treatment failure (p=0.27; data not shown). However the timing of treatment failure differed markedly according to baseline serum β₂-microglobulin levels. Among 22 patients with normal β₂-microglobulin, who failed a primary therapy, 4 (18%) did not achieve CR, 8 (36%) relapsed within one year and 10 (45%) relapsed more than one year after the end of treatment. In contrast, among 11 patients with elevated β₂-microglobulin levels who failed primary therapy, 5 (45%) did not achieve CR, 5 (45%) relapsed within one year and 1 (9%) relapsed more than one year after the end of treatment. The 4-year survival after failure was 20% for patients who did not achieve CR versus 37% for relapsed patients (p=0.06). Multivariate analysis of survival after failure demonstrated that the outcome was predicted by the failure to achieve CR (p=0.03) and age ≥45 years had borderline significance (p=0.09), while β₂-microglobulin levels were not significant.

Discussion

The present study suggests that serum β₂-microglobulin level may not be an independent biological prognostic marker for FFS in patients with HL treated homogeneously with ABVD or equivalent regimens, although it is efficient in predicting overall survival. This study is the largest reported so far regarding β₂-microglobulin in HL.

Serum β₂-microglobulin was elevated in 28% of our patients and this figure is in agreement with previous reports.[30,37,39,45] We found a statistically significant association between serum β₂-microglobulin and advanced age, B-symptoms, advanced AAS, and anemia, in accordance with previously published observations. In addition, we observed a statistically significant association between elevated β₂-microglobulin level and the number of involved anatomic sites, inguinal/iliac involvement, lymphocytopenia, elevated LDH, and high IPS. These associations were not evaluated in previous studies. Thus, it appears that serum β₂-microglobulin is correlated with several other known adverse conventional prognostic factors for HL. Furthermore, we have previously reported that serum β₂-microglobulin level is also correlated with biological prognostic factors, such as elevated serum interleukin-10 and soluble CD30 levels.[29,46]

Both univariate and multivariate analyses revealed that elevated serum β₂-microglobulin levels were not predictive of FFS in our patients treated with ABVD or equivalent regimens. In contrast serum β₂-microglobulin was an independent prognostic factor in an MD Anderson study.[39] Given the larger number of patients included in our study, our inability to demonstrate serum β₂-microglobulin as an independent prognostic factor for FFS may be attributed to the homogeneous treatment of our patients with effective regimens, since it is known that more effective treatment may eliminate the significance of previously established prognostic factors. Indeed, in the MD Anderson series, in which β₂-microglobulin was demonstrated to be an independent adverse prognostic factor, at least 60% of the patients had been treated with RT alone, MOPP plus RT or NOVP plus RT, which are inferior to ABVD-based approaches.[1,4,6,12,47] In the studies conducted by the Karolinska group and BNLI, which included fewer than 100 patients, β₂-microglobulin was not an independent prognostic factor.[30,38] Analogously most patients had received inferior treatment regimens, such as RT alone or MOPP-like regimens. In

the last reported study, β_2-microglobulin was inde-pedently associated with prognosis in 64 patients with HL.[37] Thus, the present study is the first to report that serum β_2-microglobulin may not be an independent prognostic factor for patients with HL, treated homogeneously with ABVD or equivalent regimens.

Serum β_2-microglobulin was an independent prognostic factor for OS in our patients, in aggree-ment with the finding of the MD Anderson study. This was mainly due to the effect of elevated β_2-microglobulin levels on the outcome of patients with IPS <3. We tried to explain the discrepancy between the effects of β_2-microglobulin on FFS and OS on the basis of the correlation between its lev-els and advanced age, which is associated with a higher frequency of unrelated deaths. Age did not replace β_2-microglobulin in the multivariate analy-sis of OS and β_2-microglobulin remained signifi-cant when Hodgkin's lymphoma-specific survival was considered, since the vast majority of deaths were disease-related. An alternative explanation could be based on the observation that patients with elevated β_2-microglobulin levels tended to have inferior survival after treatment failure. How-ever, as revealed by multivariate analysis, this dif-ference was largely explained by the higher inci-dence of primary resistance and early relapse of patients with elevated β_2-microglobulin levels. Thus we propose the following explanation for the dif-ferential effect of β_2-microglobulin on FFS and OS of patients with HL: although FFS curves reach a plateau at approximately the same level, the curve of patients with high β_2-microglobulin falls rapid-ly to that level early in the course of follow-up, due to the much higher incidence of primary resistant and early relapsing disease. However these patients – especially primary resistant ones – frequently have a rapidly fatal clinical course,[48-50] in contrast to late-relapsing patients (most of whom had nor-mal β_2-microglobulin in this series). Thus at this point of our study we were able to demonstrate a difference in terms of OS despite similar FFS. Pro-jecting this hypothesis, it is logical to expect that the recruitment of a substantially larger number of patients could render the difference in terms of FFS statistically significant because of the different tim-ing of treatment failure in relation to β_2-microglob-ulin levels, even though the long term FFS will prob-ably be similar for both groups.

Elevation of serum β_2-microglobulin levels may originate from increased cell turnover or increased shedding due to decreased cell surface expression.[38] Furthermore elevated β_2-microglobulin might reflect the tumor burden.[34] The biological basis underlying a potential adverse prognostic signifi-cance of elevated serum β_2-microglobulin remains obscure. Indirect information can be obtained from studies focusing on other diseases. Thus, in diffuse large cell lymphoma, absence of MHC class I expression correlates with higher serum β_2-micro-globulin levels.[51] Patients with absent MHC I expression have a particularly poor prognosis,[52] pre-sumably due to defective recognition of tumor-spe-cific antigens by cytotoxic T-cells. However, recent studies provided data suggesting a potentially favorable effect of β_2-microglobulin on the prog-nosis of hematologic malignancies.[53,54] Thus, it has been demonstrated that β_2-microglobulin is an apoptosis-inducing factor in neoplastic T-cells and myeloid leukemic cells via the activation of cas-pase-3 and nuclear factor-κB, and may regulate the elimination of tumor cells.[53,54] Whether the aforementioned observations apply to HL as well needs to be investigated.

Based on our data, serum β_2-microglobulin level is not a potent predictor of FFS in HL treated with ABVD or equivalent regimens, although a low-mag-nitude effect cannot be excluded, when substan-tially larger patient populations are analyzed. How-ever, the prognostic significance of β_2-microglob-ulin may be better with respect to OS. Further ver-ification in the context of a prospective study would be significant. Until definite data become available, serum β_2-microglobulin, which can be routinely measured in clinical practice, could be evaluated prior to treatment initiation and described as a baseline characteristic in reported series of patients with HL.

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interpreting the data, and preparing the article, while GP was study supervisor, and took responsibility for this work, from conception to submitted manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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