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 lymphomas, but only limited data suggest an adverse prognostic significance for Hodgkin’s lymphoma (HL). This study was undertaken to examine the impact of sβ2m on the prognosis of patients with HL.

Design and Methods. sβ2m was measured by a radioimmunoassay (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% 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), ≥3 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 corresponding 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 associated with inferior OS (p=0.01), along with the number of involved sites (p<0.001).

Interpretation and Conclusions. sβ2m is not a potent prognostic 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, prognostic factors, chemotherapy

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Malignant Lymphomas

research paper

haematologica 2002; 87:701-708


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 following an initial remission achieved by chemotherapy (CT) or combined modality therapy.1-12 ABVD13 is considered as a standard CT regimen, either alone or in combination with MOPP in alternating14 or hybrid schedules.1 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 prognostic models incorporating clinical and routine laboratory 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 separately.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.3-31

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.31-36

The reported series regarding the prognostic significance of β2-microglobulin in HL have reached contradictory conclusions, usually analyzing relatively small populations of patients,30,37,38 treated
with heterogeneous strategies, which were usually inferior to current standard therapy. Based on these considerations, we evaluated the frequency of elevated serum β₂-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 β₂-microglobulin levels available, and had received treatment with anthracycline-based CT with or without RT. Serum samples for β₂-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 Kapedistrian 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 β₂-microglobulin levels were not available.

Staging and routine laboratory evaluation

All patients were clinically staged according to the Ann Arbor system, using standard staging procedures. The number of involved anatomic sites was determined as described elsewhere. 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 as the 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.

Serum β₂-microglobulin determination

Serum β₂-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 (n=150). AAS IB, IIB, IIIB and IV as well as one AAS IIIA patient were treated with alternating MOPP/ABV (n=12), the MOPP/ABV hybrid regimen (n=12), or ABVD (n=58), usually without RT. All these regimens are currently considered equivalent.

Statistical analysis

The distribution of the clinical and laboratory characteristics among patients with known and unknown serum β₂-microglobulin levels and the frequency of elevated serum β₂-microglobulin levels among various subgroups of patients defined by other known prognostic factors were compared by the χ² test. 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. The identification of prognostic factors in univariate analysis was based on the log-rank test. The identification of independent prognostic factors was performed using Cox’s proportional hazards model. 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...
between the 232 patients with known and the 265 patients with unknown serum $\beta_2$-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 $\beta_2$-microglobulin levels was 29 months.

**Table 1. Comparison of presenting clinical and laboratory features between patients with known and unknown serum $\beta_2$-microglobulin levels.**

<table>
<thead>
<tr>
<th>Clinical or laboratory feature studied</th>
<th>Serum $\beta_2$-microglobulin Levels</th>
<th>Known (n=232)</th>
<th>Unknown (n=265)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td></td>
<td>30.5 (14-78)</td>
<td>30.0 (13-82)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥45 years</td>
<td></td>
<td>114/232</td>
<td>23/265</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex (male)</td>
<td></td>
<td>134/232</td>
<td>58/265</td>
<td>0.009</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td>150/225</td>
<td>72/255</td>
<td>0.67</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td></td>
<td>81/225</td>
<td>37/255</td>
<td>0.02</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td></td>
<td>47/225</td>
<td>12/255</td>
<td>0.61</td>
</tr>
<tr>
<td>Lymphocyte predominance</td>
<td></td>
<td>5/225</td>
<td>1/255</td>
<td>0.75</td>
</tr>
<tr>
<td>Lymphocyte depletion</td>
<td></td>
<td>7/225</td>
<td>1/255</td>
<td>0.14</td>
</tr>
<tr>
<td>Unclassified/unknown</td>
<td></td>
<td>7</td>
<td>7</td>
<td>0.14</td>
</tr>
<tr>
<td>B-symptoms</td>
<td></td>
<td>79/232</td>
<td>52/265</td>
<td>0.08</td>
</tr>
<tr>
<td>Ann Arbor clinical stage</td>
<td></td>
<td>55/232</td>
<td>80/265</td>
<td>0.08</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>55/232</td>
<td>80/265</td>
<td>0.08</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>114/232</td>
<td>127/265</td>
<td>0.08</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>42/232</td>
<td>54/265</td>
<td>0.08</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>21/232</td>
<td>24/265</td>
<td>0.08</td>
</tr>
<tr>
<td>Involved anatomic sites (≥5)</td>
<td></td>
<td>31/232</td>
<td>41/265</td>
<td>0.08</td>
</tr>
<tr>
<td>Inguinal and/or iliac involvement</td>
<td></td>
<td>47/230</td>
<td>49/265</td>
<td>0.08</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>80/230</td>
<td>95/265</td>
<td>0.08</td>
</tr>
<tr>
<td>Leukocytosis (≥15×10^9/L)</td>
<td></td>
<td>28/228</td>
<td>46/255</td>
<td>0.08</td>
</tr>
<tr>
<td>Lymphocytopenia (≤0.5×10^10/L)</td>
<td></td>
<td>29/208</td>
<td>22/206</td>
<td>0.08</td>
</tr>
<tr>
<td>ESR (≥50 mm the 1st hour)</td>
<td></td>
<td>79/186</td>
<td>97/206</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum albumin (≥3.5 g/dL)</td>
<td></td>
<td>19/212</td>
<td>50/161</td>
<td>0.08</td>
</tr>
<tr>
<td>LDH levels elevated</td>
<td></td>
<td>60/188</td>
<td>32/206</td>
<td>0.08</td>
</tr>
<tr>
<td>International Prognostic Score</td>
<td></td>
<td>41/215</td>
<td>54/215</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**Table 2. Correlation of serum $\beta_2$-microglobulin levels with other known prognostic factors in 232 patients with Hodgkin’s lymphoma.**

<table>
<thead>
<tr>
<th>Clinical or laboratory factor</th>
<th>Serum $\beta_2$-microglobulin &gt;3.4 mg/L (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≤45 vs ≥45)</td>
<td>19 vs 55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>30 vs 26</td>
<td>0.47</td>
</tr>
<tr>
<td>Histology (NS vs MC vs LP)</td>
<td>24 vs 44 vs 19</td>
<td>0.03</td>
</tr>
<tr>
<td>B-symptoms (no vs yes)</td>
<td>22 vs 41</td>
<td>0.002</td>
</tr>
<tr>
<td>Ann Arbor clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I vs II vs III vs IV</td>
<td>15 vs 27 vs 41 vs 43</td>
<td>0.02</td>
</tr>
<tr>
<td>I/II/III vs IV</td>
<td>27 vs 43</td>
<td>0.11</td>
</tr>
<tr>
<td>Involved anatomic sites (≥5 vs ≤5)</td>
<td>25 vs 45</td>
<td>0.009</td>
</tr>
<tr>
<td>Inguinal/iliac involvement (no vs yes)</td>
<td>24 vs 43</td>
<td>0.009</td>
</tr>
<tr>
<td>Anemia (no vs yes)</td>
<td>23 vs 36</td>
<td>0.03</td>
</tr>
<tr>
<td>White blood cells (&lt;vs ≥15×10^9/L)</td>
<td>27 vs 39</td>
<td>0.06</td>
</tr>
<tr>
<td>Lymphocytopenia (≤vs ≥0.5×10^10/L)</td>
<td>26 vs 54</td>
<td>0.002</td>
</tr>
<tr>
<td>ESR (&lt; vs ≥50 mm the 1st hour)</td>
<td>21 vs 30</td>
<td>0.13</td>
</tr>
<tr>
<td>Serum albumin (≥3.5 vs &lt; 3.5 g/dL)</td>
<td>25 vs 42</td>
<td>0.12</td>
</tr>
<tr>
<td>LDH levels (normal vs elevated)</td>
<td>23 vs 40</td>
<td>0.01</td>
</tr>
<tr>
<td>International Prognostic Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>21 vs 54</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

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 $\beta_2$-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 $\beta_2$-microglobulin levels. At 7 years, FFS was 75% vs 72% for patients with normal and elevated $\beta_2$-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 $\beta_2$-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 $\beta_2$-microglobulin levels, respectively (p=0.40). Elevated serum $\beta_2$-microglobulin level was predictive of OS, since OS at 7 years was...
86% versus 52% in patients with normal and elevated serum β₂-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 β₂-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 β₂-microglobulin levels had no independent effect on FFS. In contrast, serum β₂-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.
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.79,46

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, β2-microglobulin was independently associated with prognosis in 64 patients with HL.37 Thus, the present study is the first to report that serum β2-microglobulin may not be an independent prognostic factor for patients with HL, treated homogeneously with ABVD or equivalent regimens.

Serum β2-microglobulin was an independent prognostic factor for OS in our patients, in agreement with the finding of the MD Anderson study. This was mainly due to the effect of elevated β2-microglobulin levels on the outcome of patients with IPS <3. We tried to explain the discrepancy between the effects of β2-microglobulin on FFS and OS on the basis of the correlation between its levels and advanced age, which is associated with a higher frequency of unrelated deaths. Age did not replace β2-microglobulin in the multivariate analysis of OS and β2-microglobulin remained significant 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 β2-microglobulin levels tended to have inferior survival after treatment failure. However, as revealed by multivariate analysis, this difference was largely explained by the higher incidence of primary resistance and early relapse of patients with elevated β2-microglobulin levels. Thus we propose the following explanation for the differential effect of β2-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 β2-microglobulin falls rapidly 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 normal β2-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. Projecting 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 timing of treatment failure in relation to β2-microglobulin levels, even though the long term FFS will probably be similar for both groups.

Elevation of serum β2-microglobulin levels may originate from increased cell turnover or increased shedding due to decreased cell surface expression.38 Furthermore elevated β2-microglobulin might reflect the tumor burden.34 The biological basis underlying a potential adverse prognostic significance of elevated serum β2-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 β2-microglobulin levels.51 Patients with absent MHC I expression have a particularly poor prognosis, presumably due to defective recognition of tumor-specific antigens by cytotoxic T-cells. However, recent studies provided data suggesting a potentially favorable effect of β2-microglobulin on the prognosis of hematologic malignancies.53,54 Thus, it has been demonstrated that β2-microglobulin is an apoptosis-inducing factor in neoplastic T-cells and myeloid leukemic cells via the activation of caspase-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 β2-microglobulin level is not a potent predictor of FFS in HL treated with ABVD or equivalent regimens, although a low-magnitude effect cannot be excluded, when substantially larger patient populations are analyzed. However, the prognostic significance of β2-microglobulin may be better with respect to OS. Further verification in the context of a prospective study would be significant. Until definite data become available, serum β2-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.

Contributions and Acknowledgments

TPV was primarily responsible for this work from conception to submitted manuscript, and should be considered as the principal author. All authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria, and have taken specific responsibilities, as described below: TPV: statistical analysis; GN: laboratory experiments; TPV, MKA: collection of data; GAP, TPV, MKA, MPS, M ND, FNK, CK, SIK, M CK, PT: management of clinical data covering a long follow-up period; GAP, GP: study supervisors, responsibility from conception to submitted manuscript, and final approval of the manuscript. All authors contributed to the writing of the paper. The authors are listed according to a criterion of decreasing individual contribution to the work, with the following exceptions: the last author had a major role as senior author in designing the study,
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.

References
25. Haematologica vol. 87(7): july 2002

The clinical role and prognostic importance of β2-microglobulin in Hodgkin's disease is associated with lower progression-free survival and blood. Blood. 2000; 96 Suppl 1:725a (abstract).


What is already known on this topic

The clinical role and prognostic importance of β2-microglobulin in Hodgkin's lymphoma is still unclear and strongly debated.

What this study adds

The study points out that serum β2-microglobulin did not exert an independent prognostic power in relation to failure-free survival while it did against overall survival.

Potential implications for clinical practice

The reasons for such a discrepancy, that can explain some contradictory results of the literature, were not approached but only hypothesized. However, this work may represent a useful clue for future investigations that will try to clarify the unsolved matter of the true clinical significance of β2-microglobulin in Hodgkin's lymphoma.