Prognostic Role of Serum β_2-Microglobulin in Hodgkin's Disease

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Purpose: **To evaluate the role of serum β_2-microglobulin (β2M) in the prognosis of patients with Hodgkin's disease.**

Patients and Methods: **One hundred sixty previously untreated patients with Hodgkin's disease had serum β2M levels determined before initiation of treatment. Serum β2M was tested for its correlation with known prognostic factors for patients with Hodgkin's disease. These variables, including β2M, were correlated with complete remission (CR) rate and time to treatment failure (TTF). Univariate and multivariate analyses were performed.**

Results: **Serum β2M levels greater than 2.5 mg/L were found in 29% of patients. Such elevation was more common in patients with more advanced-stage disease. Elevated serum β2M was an independent and powerful factor in the prediction of lower response rate and shorter TTF. Its impact appeared to be more significant in patients with advanced disease.**

Conclusion: **Serum β2M appears to correlate with tumor stage in patients with Hodgkin's disease and elevated serum levels of this polypeptide predict a less favorable prognosis.**

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THE LIGHT-CHAIN molecule of the major histocompatibility complex class I antigen is represented by β_2-microglobulin (β2M), a low–molecular weight, single polypeptide chain of 100 amino acids.[1] β2M is found on the cytoplasmic membrane of almost all nucleated cells; the membrane turnover is the principal source of β2M in the blood and body fluids. Serum levels of β2M are increased in a wide range of malignant and nonmalignant diseases.

Elevated serum levels of β2M have been associated with poor prognosis in patients with several lymphoid malignancies, including multiple myeloma, large-cell lymphoma, and low-grade lymphomas.[2-4] The significance of this marker in patients with Hodgkin's disease has not been well established. In this analysis of 160 previously untreated patients with Hodgkin's disease, we demonstrated that an elevated serum level of β2M is a significant prognostic factor associated with a lower complete remission rate and a shorter time to treatment failure (TTF).

PATIENTS AND METHODS

Over the last 5 years, serum β2M levels were determined before initiation of treatment in 160 previously untreated patients with Hodgkin's disease who constitute the cohort analyzed in this study. Histologic classification of initial surgical material was made according to the Rye modification of the Lukes and Butler scheme.[5] All patients were staged according to the Ann Arbor staging system.[6] Initial evaluation included a complete history and physical examination, chest roentgenograms, computed tomographic (CT) scans, bipedal lymphangiograms, bilateral bone marrow aspirates and biopsies, and routine laboratory blood studies including serum β2M levels. Measurement of serum β2M was performed using a Pharmacia β2 micro RIA (Pharmacia Diagnostics, Upsala, Sweden) radioimmunoassay.

Treatment

Among the 90 patients with clinical stage I and II disease, 34 were identified to have stage I or II disease after laparotomy and splenectomy and subsequently were treated with radiotherapy only as previously described.[7] The remaining 56 patients received limited chemotherapy followed by involved-field radiotherapy according to several treatment protocols.[8-10] Forty-two patients had stage III disease and were treated either with limited chemotherapy followed by involved-field radiotherapy when no B symptoms were present, or with chemotherapy alone for symptomatic patients. All 28 patients with stage IV disease received combination chemotherapy as previously described.[11]

Statistics

Serum β2M was tested for its correlation with known prognostic variables in patients with Hodgkin's disease.[12-15] These variables, including β2M, were evaluated for their role in predicting the probability of a complete remission, as well as TTF, which has been previously defined as the time from the beginning of treatment to removal from study either because of progression of disease or toxic or tumor-related death.[16] TTF curves were constructed using the method of Kaplan and Meier[17] and statistical significance was determined with the generalized Wilcoxon test.[18] Both univariate and multivariate analyses of the TTF data using the Cox proportional hazards model were performed to assess the importance of eight factors: age, sex, hemoglobin, serum β2M, Ann Arbor stage, histologic subtype, presence of B symptoms, and presence of mediastinal mass as determined by plain chest roentgenograms.[19] A multivariate logistic analysis was performed to identify independent factors that predict response. The χ^2 test was used to compare frequencies.

RESULTS

Clinical Characteristics

The mean and median serum β2M levels were 2.1 mg/L and 1.9 mg/L, respectively (range, 0.2 to 5.5 mg/L). No

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Table 1. Correlation of β2M Serum Levels With Clinical and Laboratory Features

Variable	No. of Patients	% of Patients With β2M ≤ 2.5 mg/L	% of Patients With β2M > 2.5 mg/L	P
Sex				
Female	68	71	29	.99
Male	92	71	29	
Age, years				
≤ 50	135	78	22	< .001
> 50	25	32	68	
Ann Arbor stage				
I	24	88	12	
II	66	85	15	< .001
III	42	57	43	
IV	28	43	57	
Symptoms				
A	117	79	21	< .001
B	43	49	51	
Histology				
Nodular sclerosis	110	72	28	.62
Other	50	68	32	
Mediastinal mass				
None	51	73	27	.65
< 7.5 cm	43	65	35	
≥ 7.5 cm	66	73	27	
Hemoglobin, g/dL				
Male				
≥ 12.5	71	77	23	
< 12.5	21	48	52	.008
Female				
≥ 11.0	56	73	27	.31
< 11.0	12	58	42	

patient had elevated serum creatinine that could account for an abnormal serum β2M level. Results of data analysis treating β2M as a continuous variable were the same as those treating β2M as a dichotomous variable when 2.5 mg/L was used as a cutoff point. Thus, a serum β2M cutoff value of 2.5 mg/L (upper limit of normal, 2.0 mg/L) was used to separate patients into low and high serum β2M groups for data analysis and construction of TTF curves.

Among 160 previously untreated patients, 47 (29%) had elevated serum β2M levels greater than 2.5 mg/L. Table 1 shows the correlation of serum β2M levels with clinical and laboratory features of patients with Hodgkin's disease. Elevated serum β2M values were more common in older patients, in patients with B symptoms, in those with more advanced Ann Arbor stage, and in male patients with lower hemoglobin values.

Response and TTF

Of 160 patients, 142 (89%) achieved a complete remission (CR), defined as complete disappearance of all evidence of disease; the remaining patients achieved either a partial response (11 patients), stable disease (four patients), or progressed during treatment (two patients). One patient could not be assessed for response. The CR rate was lower in patients with elevated β2M levels when compared with those with low β2M levels (93% *v* 79%; $P = .01$). Other factors, such as sex, age, stage, B symptoms, histology, presence of mediastinal mass, and hemoglobin, were not predictive for CR.

Table 2. Cox Regression Analysis for TTF (univariate analysis)

Variable	Coefficient	SE	P
β2M	0.64	0.17	< .001
Hemoglobin	− 1.11	0.42	.009
Ann Arbor stage	0.46	0.21	.03
Histology	0.06	0.1	.55
B symptoms	0.39	0.41	.33
Mediastinal mass	0.11	0.22	.61
Age	0.01	0.01	.42
Sex	0.32	0.38	.40

With a median follow-up duration of 30 months, 25 patients (16%) have failed. Table 2 lists the results of univariate analyses in which several prognostic variables and serum level of β2M were examined. All interval variables were included as continuous, rather than dichotomous; thus, we entered the exact value for β2M, age, and hemoglobin. The variables that predicted shorter TTF were high serum β2M, low hemoglobin, and advanced Ann Arbor stage. The results of the univariate analysis remained the same when serum β2M and hemoglobin were used as dichotomous variables. Stepwise Cox repression analysis was used for the multivariate analyses including all partial covariates in one model. After including β2M, all other covariates became nonsignificant. Since the value of hemoglobin depends on gender, Table 3 lists the results of a Cox repression analysis including β2M and hemoglobin as covariates. It is clear that β2M remained an important covariate in both male and female patients. After conditioned on the β2M value, hemoglobin was not significant. We also analyzed the interaction of β2M and hemoglobin and found no significant association.

Figure 1 shows the TTF of patients with either low or

Table 3. Cox Regression Analysis for TTF (multivariate analysis) by Sex

Variable	Coefficient	SE	P
Male			
β2M	0.53	0.25	.04
Hemoglobin	− 0.09	0.12	.46
Female			
β2M	0.76	0.35	.03
Hemoglobin	− 0.29	0.18	.12

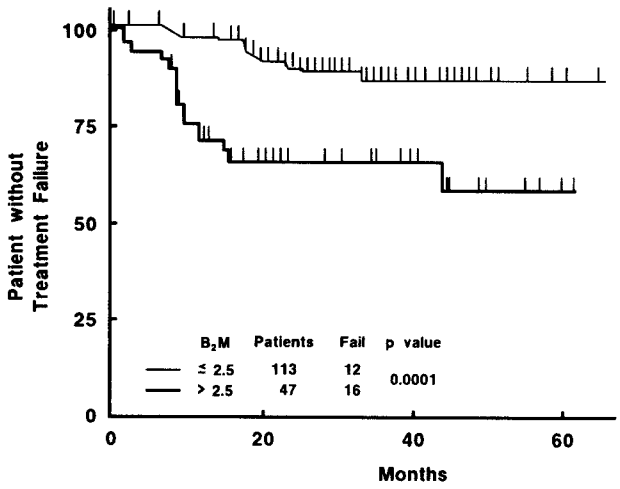

Fig 1. TTF in patients with Hodgkin's disease in relation to serum β2M.

high levels of serum β2M. Patients with low-level β2M had a significantly better prognosis than patients with high-level β2M. Furthermore, the impact of β2M serum levels on the TTF was assessed separately for patients with stages I or II disease and those with stages III or IV disease. As shown in Fig 2, elevated β2M values were correlated with a significantly higher relapse rate in patients with advanced-stage disease (Fig 2B) than in patients with low-stage disease (Fig 2A).

DISCUSSION

β2M is an important prognostic factor in patients with several lymphoproliferative disorders. Studies in patients with multiple myeloma have shown that elevated serum β2M levels correlate with high tumor load and have an adverse association with survival.[2] In a similar manner, β2M was found to be an important factor predicting shorter TTF and survival in patients with intermediate-grade and low-grade lymphomas.[3,4]

Few studies have assessed the prognostic significance of this molecule in patients with Hodgkin's disease.[20-22] We examined the value of β2M in a large number of previously untreated patients with this malignancy. Our exploratory study shows that the incidence of elevated β2M was higher in older patients, those with more advanced stage, and those with B symptoms. The correlation of elevated serum levels of β2M with more advanced disease and B symptoms has been reported previously, and our study confirmed this observation in a larger number of patients.[20-22] Although the underlying pathophysiologic mechanism that results in the elevation of serum β2M is not clear, there is evidence that tumor cells release this substance through membrane turnover. Thus, β2M could serve as a tumor marker and may reflect tumor burden in patients with Hodgkin's disease. It is also possible that serum β2M levels reflect the metabolic activity of a more rapidly proliferating population of tumor cells.

We also found that pretreatment level of serum β2M is a powerful predictor of clinical outcome as measured by CR rate and TTF. Patients with lower pretreatment levels of β2M had a significantly higher CR rate than those with higher β2M levels, as well as a longer TTF. This observation was valid when β2M was used either as a continuous variable or as a dichotomous factor with several cutoff levels. Previous studies have shown that elevated serum β2M was associated with shorter survival, especially in patients with widespread disease.[20,21] Longer follow-up of our patients is required to assess whether

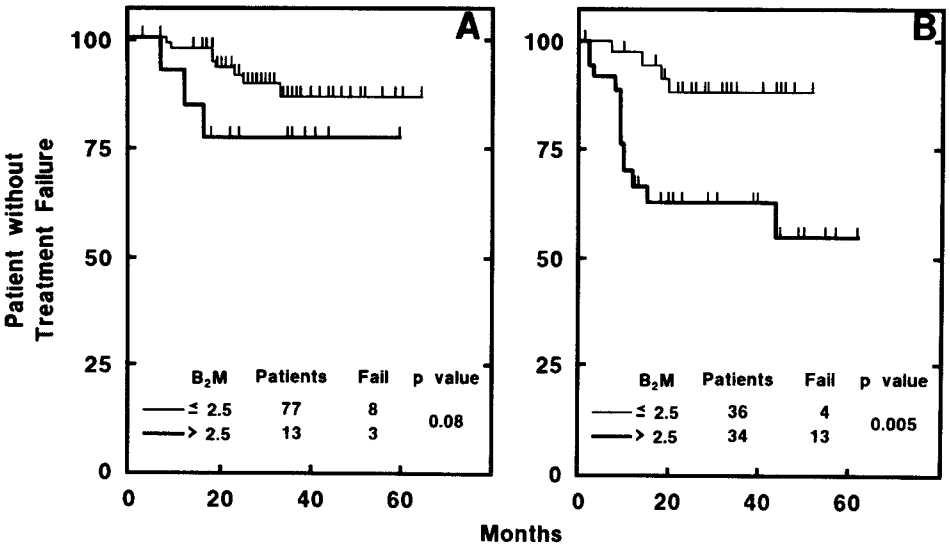

Fig 2. TTF in patients with (A) stage I and II disease and (B) stage III and IV disease in relation to serum β2M.

serum β2M levels correlate with overall survival. Evaluation of β2M also seems worthy of study in patients with relapsed Hodgkin's disease who are receiving salvage regimens, including bone marrow transplantation, since we suspect that a higher proportion of such patients will have elevated serum levels of this polypeptide.

The definitive establishment of β2M as a prognostic factor for patients with Hodgkin's disease will require confirmation in a prospective study. If the significance of β2M can be confirmed, the objective and reproducible nature of the assay used to measure this substance makes it an attractive tool that can be used to help compare interinstitutional data. Furthermore, its correlation with other significant prognostic factors, such as the erythrocyte sedimentation rate, is desirable.[23]

The impact of elevated serum levels of β2M appeared to be more significant in patients with stage III and IV Hodgkin's disease, since almost one half of patients with both advanced disease and high serum β2M have relapsed. Thus, β2M may serve as a marker of adverse prognosis in patients with advanced Hodgkin's disease and may identify at diagnosis a subgroup of patients that should be considered for intensive consolidation, such as with bone marrow transplantation.

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