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Serum Beta-2 Microglobulin as Biomarker in Chronic Lymphocytic Leukemia

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Abstract

Background: Beta-2 microglobulin (B2M) has been identified for many years as a reliable prognostic marker in patients with chronic lymphocytic leukemia (CLL). Our study aimed to determine the serum level of B2M in Sudanese CLL patients and correlate it with other clinical and hematological parameters.

Methods and Results: A cross-sectional study was conducted at the Radio Isotopes Centre of Khartoum in Sudan. Forty-six patients previously diagnosed with CLL were enrolled in the study, and 14 healthy individuals were also included to control the assessment of B2M. Out of the 46 CLL patients (30 men and 16 women), 32 patients underwent chemotherapy treatment, while 14 patients were untreated and newly diagnosed. Complete blood count was measured using Sysmex KX-21N-TOA. The serum B2M level was measured using solid-phase sandwich ELISA.

The absolute lymphocyte count was 31.3±26.8 ($\times 10^9$/L), with lymphocytosis in 93.8%. The mean platelet count was 158.5±66.4 ($\times 10^9$/L), and thrombocytopenia was noticed in 25% of the patients. The serum level of B2M was significantly higher in CLL than in healthy normal controls (7.9±6.1 mg/L versus 0.6±0.3 mg/L, P=0.000). In CLL-untreated patients, the B2M level was also significantly higher than in treated patients: 18.1±5.2 mg/L versus 5.5±3.0 mg/L (P<0.0001). The B2M level was significantly higher in patients at stages III and IV than in stages I and II: 8.6.1±5.1 mg/L versus 2.7±0.3 mg/L (P<0.0001).

Conclusion: Serum B2M level correlates with the disease stages in CLL patients, and its determination could be useful in following up on CLL patients during the treatment or remission.**(International Journal of Biomedicine. 2024;14(4):591-594.)**

Keywords: beta-2 microglobulin • chronic lymphocytic leukemia • complete blood count

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Abbreviations

B2M, beta-2 microglobulin; **CLL**, chronic lymphocytic leukemia, **CBC**, complete blood count.

Introduction

Chronic lymphocytic leukemia CLL has a clinical heterogeneous course of disease. Some patients show indolent disease and never need treatment, while others require intensive treatment early after diagnosis.[1] The clinical stage developed by Rai and Binet remains the strongest predictor of survival in patients with CLL.[2] In the last 10 years, several prognostic markers that go beyond clinical staging and may offer helpful prognostic information to CLL patients have been discovered and assessed. These prognostic markers include IGHV mutational status, chromosomal aberrations [del(13q), del(11q), del(17p)], CD38 expression, CD49d, and ZAP-70 expression/methylation, and serum markers (e.g., thymidine kinase and beta-2 microglobulin).[3]

Serum, urine, and synovial fluid are among the biological fluids that include beta-2 microglobulin (B2M), a tiny protein that has a molecular weight of 11,800 Dalton. B2M is found in

almost all nucleated cells.[4] Besides its role in immunity, B2M has been shown to have various other clinically significant effects, such as regulating cancer cell survival, proliferation, metastasis, and even apoptosis.[5-7]

Elevated levels of plasma B2M indicate either its glomerular filtration reduction or an increase in synthesis due to membrane turnover. The increased plasma B2M levels have been documented in several hematologic malignancies, including multiple myeloma, lymphomas, myelodysplastic syndromes, chronic myeloid leukemia and CLL.[8-14] Some reports indicate that raised B2M is a predictor of poor survival in several of these malignancies.

B2M analysis is a cheap test that does not require advanced machines or equipment; hence, it can be investigated in an average routine laboratory. Therefore, the present study aims to determine B2M level in serum of CLL patients as a biological prognostic marker.

Materials and Methods

A cross-sectional study was conducted at the Radio Isotopes Centre of Khartoum in Sudan. Forty-six patients previously diagnosed with CLL were enrolled in the study, and 14 healthy individuals were also included to control the assessment of B2M. A CLL diagnosis was made by specialized oncologists in the center, based on the clinical examination, morphology, and standard immunophenotyping.

Out of the 46 CLL patients (30 men and 16 women), 32 patients underwent chemotherapy treatment, while 14 patients were untreated and newly diagnosed. The demographic data were collected by direct oral interviewing, and clinical data was collected from the patient's medical record and a questionnaire. From each enrolled subject, venous blood samples (3 ml) were collected. Complete blood count (CBC) was measured using Sysmex KX-21N-TOA (Medical Electronics Company, Japan). The serum B2M level was measured based on the principle of a solid phase ELISA method according to manufacturer guidelines. B2M values greater than 2.4 mg/L were considered elevated.[15]

Statistical analysis was performed using the statistical software package SPSS version 20.0 (SPSS Inc, Armonk, NY: IBM Corp). Baseline characteristics were summarized as frequencies and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. Inter-group comparisons were performed using Student's t-test. Group comparisons concerning categorical variables were performed using chi-square or Fisher's exact tests. A *P*-value of <0.05 was considered statistically significant.

Results

The mean age of the study patients was 58.5 years. Sixteen of the patients were at stage III, while the rest were distributed equally with 10 cases in each stage: I, II and IV. Thirty-two participants (69.6%) were started on treatment at the time of enrollment, and 14(30.4%) were untreated.

In CLL patients, the mean hemoglobin level was 9.7±2.2 g/dL, with an anemia frequency of 81.2%. The absolute lymphocyte count mean was 31.3(±26.8)×10^9/L, with absolute lymphocytosis in 93.8%. The mean platelet count was 158.5(±66.4)×10^9/L, and thrombocytopenia was noticed in 25% of the patients (Table 1).

Table 1.

Demographic, clinical and hematological characteristics of CLL patients.

Variable	Patients (n=46)
Gender, M/F	30/16
Age (year), mean (range)	58.5 (40-76)
Hemoglobin (g/dL), mean ± SD	9.7±2.2
Lymphocyte, (×10^9/L), mean ± SD	31.3± 26.8
Platelet count (×10^9/L), mean ± SD	158.5±66.4
B2M (mg/L), mean ± SD	7.9±6.1
Disease stage, n (%) I-II III-IV	 20 (43.5) 26 (56.5)
Treatment status, n (%) Treated Untreated	 32 (69.6) 14 (30.4)

The serum level of B2M was significantly higher in CLL than in healthy normal controls (*P*=0.000): 7.9±6.1 mg/L versus 0.6±0.3 mg/L. In CLL-untreated patients, the B2M level was also significantly higher than in treated patients: 18.1±5.2 mg/L versus 5.5±3.0 mg/L (*P*<0.0001). The B2M level was significantly higher in patients at stages III and IV than in stages I and II: 8.6.1±5.1 mg/L versus 2.7±0.3 mg/L (*P*<0.0001) (Table 2, Figure 1). In addition, there was a significant correlation between the serum level of B2M and hemoglobin concentration (r=-0.73, *P*<0.05), absolute lymphocyte count (r=0.77, *P*<0.05), and platelet count (r=-0.79, *P*<0.05).

Table 2.

B2M in groups of CLL patients.

Group	B2M	*P*-value
Treated CLL patients (n=32) Untreated CLL patients (n=14)	5.5±3.0 18.1±5.2	<0.0001
CCL stage I-II (n=20) CCL stage III-IV (n=26)	2.7±0.3 8.6±5.1	<0.0001

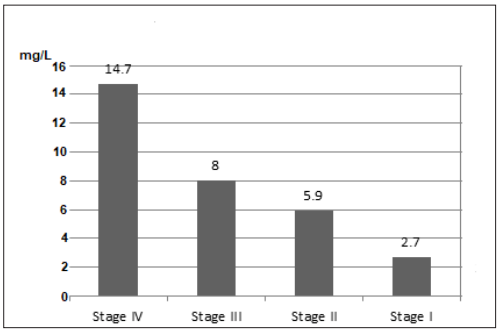

Fig. 1. *Mean B2M (mg/L) levels in CLL patients with different disease stages.*

Discussion

B2M is a serum marker and correlates with disease stage and tumor burden in patients with CLL. Gentille et al.[15] that the cut-off value of B2M that could discriminate between CLL patients whose disease progressed and those with stable disease was 2.4 mg/L. In our study, all enrolled CLL patients had elevated B2M levels with the mean of 7.9 mg/L. This finding is comparable to a study by Alrayes and Albaset,[16] where the mean of B2M was 6mg/L. B2M is constantly shed by lymphocytes, and it is expected that its levels steadily increase with the progressive expansion of the leukemic clone, suggesting a close correlation between the clinical stage and B2M levels in CLL.[15] Di Giovanni et al.[17] found that the B2M mean value in the CLL group was significantly higher than in the control group. The elevated B2M may be secondary to increased proliferation of lymphoma cells because stimulation by cytokines causes an increase in the turnover of the membrane-bound B2M.[18]

In CLL, B2M levels correlate with tumor mass, and elevated levels predict resistance to chemotherapy.[19] A significant reduction in B2M level is seen after treatment, whereas its increase could indicate a relapse. Serum B2M determination is therefore useful in follow-up, either during treatment or remission.[20] Our study's findings also revealed that serum B2M is significantly higher in the group of untreated CLL patients than in treated ones. The mean B2M was higher in untreated patients than in treated patients. Ibrahim et al.[21] reported that serum levels of B2M greater than 4.0 mg/L are adverse prognostic factors in a wide range of lymphoid malignancies, including B-CLL. Although a correlation between B2M and the disease stage in CLL likely exists, in a study by Gentile et al.,[15] there was a substantial proportion of patients with high B2M levels already at Binet A stage (low tumor burden). Also, a retrospective series of 302 untreated patients from MD Anderson Cancer Center showed that B2M was the strongest predictor of 5-year survival in a multivariate analysis that controlled for age, stage, and performance status (5-year survival for Rai stages I-II with elevated B2M = 54 months vs. 116 months for patients without elevated B2M).[22] Both studies recommended that the role of B2M as a prognostic tool should be re-evaluated, possibly in prospective studies involving larger patient cohorts. In the present study, a statistically significant elevation between stages of disease was found, as serum B12 levels elevated steadily with the stage of the disease. Fayad et al.[23] reported that elevated Rai stage and elevated B2M correlated with shorter survival in CLL patients.

In conclusion, B2M level is a simple, feasible, and cheap laboratory marker. It correlates with the disease stages in CLL patients, and its determination could be useful in following up on CLL patients during the treatment or remission. Further prospective studies with larger patient cohorts to validate the findings and fully establish the prognostic value of B2M in CLL are needed.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee at the Ministry of Health (Sudan). All participants provided written informed consent.

Competing Interests

The authors declare that they have no competing interests.

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