# Beta-2 Microglobulin as Prognostic Marker in Multiple Myeloma

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**Objectives:** A number of biological, cytogenetic, molecular and clinical factors influence the evolution of patients with multiple myeloma. The study intends to evaluate prognostic value of beta-2 microglobulin in terms of survival of patients and response to chemotherapy and correlation with the main biological factors.

**Material and method:** The study analyses 44 patients diagnosed and treated between January 2006 and December 2010. Statistical analysis consisted of calculating correlation coefficient „r" (Pearson Bravais) and survival analysis using Kaplan-Meier curves.

**Results:** Beta-2 microglobulin was directly correlated with creatinine, hypercalcemia, percentage of bone marrow plasma cells, hyperproteinemia, monoclonal gradient, immunoglobulin G and inversely correlated with haemoglobin and low serum albumin.

Median survival at patients having beta-2 microglobulin <3.5 mg/l was of 48 months, of 43 months at those having beta-2 microglobulin between 3.5 and 5.55 mg/l and 20 months at patients having beta-2 microglobulin >5.5 mg/l.

Patients with beta-2 microglobulin <5.5 mg/l had complete remission in 52.38% of cases and 4.76% of patients did not respond to treatment as compared to patients having beta-2 microglobulin >5.5 mg/l, who had complete remission in 39.13% of cases while 30.43% showed no response. Median survival of patients with beta-2 microglobulin >5.5 mg/l was of 56 months at patients who completely responded to chemotherapy and of 4 months at no responsive patients.

**Conclusions:** The high level of beta-2 microglobulin is a negative prognostic factor in the evolution of multiple myeloma patients, adversely influencing therapeutic response rates and reducing the survival of patients with multiple myeloma.

**Keywords:** multiple myeloma, beta-2 microglobulin, survival, prognostic factors

## Introduction

Multiple myeloma (MM) is a clonal late B-cell disorder in which malignant plasma cells expand and accumulate in the bone marrow, and is characterized by paraprotein production, bone lesions, anaemia, hypercalcemia, susceptibility to infections and renal impaired. MM is a heterogeneous disease with some patients dying within a few weeks of diagnosis, whereas others live for longer than 10 years, although the median overall survival is between 3 and 4 years [1–6].

Beta-2 microglobulin (β-2M) is a serum marker of tumour burden in lymphoid malignancies, including MM. For many years, the most important prognostic factor for MM has been the level of the serum β-2M. In some studies, it was shown that β-2M was a reliable marker in evaluating the presence of tumour mass, response to chemotherapy and survival [7–13].

The purpose of this study is to evaluate prognostic value of β-2M in terms of patient survival and response to chemotherapy, correlation with biological factors such as percentage of plasma cells, haemoglobin, low serum albumin, creatinine, hypercalcemia, hyperproteinemia, monoclonal gradient and immunoglobulin G.

## Material and method

the study is retrospective and it includes 44 patients diagnosed and treated in the Medical Clinic I, Haematology Department of Emergency Hospital Mures Tirgu Mures between January 2006–December 2010. The criteria for including the patients in the study were: patients aged between 35 and 90 diagnosed with MM based on proliferation of plasma cells in bone marrow, serological analysis (analysis of proteinemia, serum gamma globulins, immunoglobulin classes, ± presence/absence of Bence Jones proteinuria) and bone lesions. The staging of patients was performed using the Salmon and Durie staging system. Lower limit of the serum β-2M was considered 1.73 mg/l.

Complete response to chemotherapy was considered based on the disappearance of myelomatous protein from the serum, the Bence Jones proteinuria and the absence of the monoclonal plasma cells in the bone marrow. Partial response to chemotherapy was established when monoclonal component of the serum dropped by over 50%, when Bence Jones proteinuria decreased by over 90% and when the presence of plasma cells in the bone marrow was below 5%.

Descriptive analysis of cases was performed. Statistical analysis consisted of calculating correlation coefficient „r" (Pearson-Bravais) and survival analysis using Kaplan Meier curves. These were performed using Graph Pad Prism program, p value < 0.05 was considered statistically significant. Since the study was performed retrospectively, by analysing the data in the source documents, an informed consent was not available.

## Results

The group includes 24 men and 20 women, the average age being of 63 years. Depending on the type of immunoglob-

**Table I. The characteristics of patients having multiple myeloma**

| Characteristics | No. of patients | % |
|---|---|---|
| Age | 63 (38–88) | – |
| Sex: male / female | 24 / 20 | 54.54 / 45.45 |
| Residence: urban / rural | 21 / 23 | 47.72 / 52.27 |
| Sub-type of MM | | |
| IgG-type MM | 29 | 65.90 |
| IgA-type MM | 11 | 25.00 |
| Micromolecular MM | 3 | 6.81 |
| Nonsecretory MM | 1 | 2.27 |
| Clinical stage Salmon Durie | | |
| Stage I | 3 | 6.81 |
| Stage II | 7 | 15.90 |
| Stage III | 34 | 77.27 |
| Hemoglobin < 9 g/dl | 21 | 47.72 |
| Plasma cells > 50% | 16 | 36.36 |
| Creatinine > 1.5 mg/dl | 17 | 38.63 |
| Lytic bone lesions | 25 | 56.81 |

ulin secreted, there were IgG 65.90% of cases, IgA 25.00% of cases, micromoleculary MM 6.81% of cases and nonsecretory MM 2.27% of cases. The characteristics of patients with serum β-2M are presented in Table I. A rate of 77.27% of patients were in stage III according to the Salmon and Durie system. Bence Jones proteinuria was present in 24 patients (54.54%). Hypercalcemia was present in 25.00% of cases while low serum albumin levels were present in 50.00% of cases. Out of the investigated group of 44 patients, 26 patients (59.09%) were initially diagnosed by haematology department, 6 patients (13.63%) by rheumatology department, 3 patients by gastroenterology department and 9 patients by other departments. Performance status (ECOG) of the patients was evaluated as follows: ECOG 1 in 16 patients, ECOG 2 in 8 patients, ECOG 3 in 15 patients and ECOG 4 in 5 patients.

Depending on the level of β-2M, 22.72% of cases (10 patients) had β-2M < 3.5 mg/l, 25.00% of cases (11 patients) had β-2M between 3.5 mg/l and 5.5 mg/l and 52.27% of cases (23 patients) had β-2M > 5.5 mg/l (Figure 1).

Correlation coefficient "r" between β-2M and the percentage of plasma cells from bone marrow (plasma cells > 50%) was +0.524 (moderate direct association) considered statistically significant (p = 0.037). When we compare values of β-2M and serum creatinine level (creatinine > 1.5 mg/dl) we observed a strong direct association (r = +0.630) statistically significant (p = 0.006). Correlation coefficient between β-2M and haemoglobin level (haemoglobin < 9 g/dl) was r = -0.757 (strong inverse association) considered statistically significant (p < 0.001). Correlating the values of β-2M and low serum albumin level (albumin < 3.4 g/dl) we noticed a strong inverse association (r = -0.634) statistically significant (p = 0.002). The relationship between β-2M and hyperproteinemia was a moderate direct association (r = +0.592) considered statistically significant (p = 0.007). Correlation coefficient between β-2M and hypercalcemia was r = +0.649 (strong direct association) statistically significant (p = 0.030). Correlating the values of β-2M with immunoglobulin G level, a moderate direct association was detected (r = +0.484) statistically significant (p = 0.007). Correlation coefficient between the value of β-2M and the monoclonal gradient was r = +0.548 (moderate direct association) statistically significant (p = 0.003). The median survival for patients with normocytic normochromic anaemia was of 20 months, at patients with renal impairment being of 18 months.

**Table II. Therapeutic response rates following chemotherapy depending on β-2M upon diagnosis**

| Therapeutic response | β-2M < 5.5 mg/l (N = 21) | β-2M > 5.5 mg/l (N = 23) | Total (N = 44) |
|---|---|---|---|
| RC | 11 (52.38%) | 9 (39.13%) | 20 (45.45%) |
| RP | 9 (42.85%) | 7 (30.43%) | 16 (36.36%) |
| NR | 1 (4.76%) | 7 (30.43%) | 8 (18.18%) |

For patients with β-2M < 3.5 mg/l the median survival was 48 months (between 15 months and more than 60 months). Median survival of patients with β-2M between 3.5 mg/l and 5.55 mg/l was 43 months (between 13 months and more than 60 months). At patients with β-2M > 5.5 mg/l, median survival was 20 months (between 6 and more than 60 months) (p = 0.616) (Figure 2).

Assessed patients underwent the specific polychemotherapy treatment: MP combination (melphalan/alkeran + prednisone) in 7 patients; VAD type (vincristine + adriamycin + dexamathasone) in 32 patients; VMPC type (vincristine + melphalan + cyclophosphamide + dexamatasone) in 2 patients and Velcade in 3 patients.

Complete response to chemotherapy was present in 20 cases (45.45%), partial response in 16 cases (36.36%) and no response disease in 8 patients (18.8%). Relapse of the disease occurred in 16 cases. At patients with β-2M < 5.5 mg/l complete response to therapy occurred in 52.38% of cases (survival being between 15 and more than 60 months), partial response to therapy in 42.85% of cases (survival being between 8 and more than 28 months) and no response to therapy in 4.76% of cases. Patients with β-2M > 5.5mg/l had complete remission in 39.13% of cases, partial remission in 30.43% of cases and 30.43% of patients did not respond to treatment (Table II). Patients with β-2M > 5.5 mg/l who completely responded

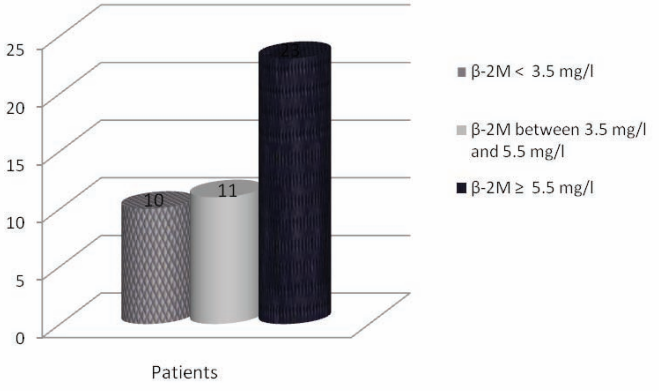


**Fig. 1. The repartition of patients according to the level of serum beta-2 microglobulin**

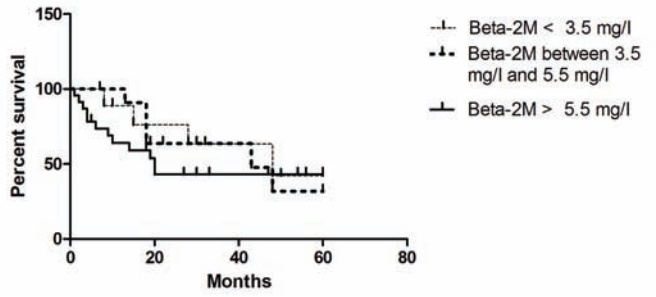


Fig. 2. Survival curve at patients with multiple myeloma depending on the level of beta-2 microglobulin

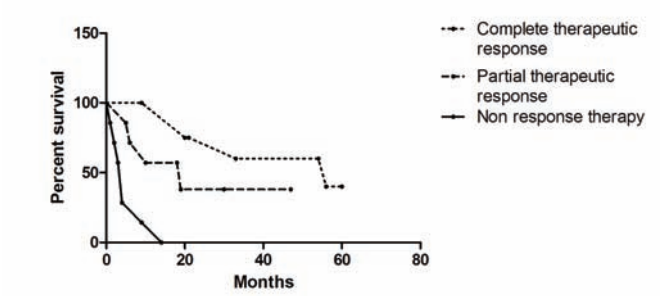


Fig. 3. Survival curve at patients with multiple myeloma and beta-2 microglobulin > 5.5 mg/l depending on response to therapy

to chemotherapy had a median survival of 56 months (between 20 and more than 60 months), patients who partially responded to chemotherapy had a median survival of 19 months (more than 6 and less than 47 months) and in the case of patients who did not respond to chemotherapy the median survival was of 4 months (between 1 and 14 months) ($p < 0.001$) (Figure 3).

## Discussions

In this study, β-2M was directly correlated with creatinine, hypercalcemia, percentage of bone marrow plasma cells, hyperproteinemia, monoclonal gradient, immunoglobulin G and inversely correlated with haemoglobin and low serum albumin.

Research performed on a group of 94 patients respectively 124 patients with MM revealed a moderate direct correlation between β-2M and the percentage of plasma cells, a strong direct association with creatinine respectively an inverse weak/moderate association with haemoglobin [10,11]. An inverse correlation resulted from the relationship between β-2M and haemoglobin on a group of 41 patients respectively direct correlations between β-2M and the volume of tumour cell mass, serum calcium level, creatinine and myeloma immunoglobulin [14].

Recently, an International Staging System (ISS) has been validated, based on the serum level of β-2M and albumin. Patients with β-2M < 3.5mg/l and albumin > 3.5g/dl (ISS stage I) had the mean survival of 62 months, considered to have a favourable prognosis. If the level of β-2M > 5.5 mg/l (ISS stage III), mean survival was of 29 months, patients being considered to have a poor prognosis. Patients classified in stage II ISS, with β-2 between 3.5 mg/l and 5.5 mg/l, had a mean survival of 44 months, considered to have an intermediate prognosis [3,5,6,12].

In our study, by grouping patients according to the level of serum β-2M, we obtained a median survival of 48 months at patients with β-2M < 3.5mg/l, 43 months at patients with β-2M between 3.5 mg/l and 5.5 mg/l, and 20 months at patients with β-2M > 5.5 mg/l. Median survival of patients in diverse studies depends on β-2M as follows: in the study on 547, for patients with β-2M < 6 μg/ml median survival was of 36 months and for those with β-2M > 6 mg/ml median survival being 23 months [9]. On another group of patients with β-2M < 4 mg/l median survival was of 65 months and for the patients with β-2M > 4 mg/l it was of 9 months [14].

For many years the most important prognostic factor has been the serum level of β-2M which shows the presence of tumour mass and renal function at patients with MM [12]. The serum level helps us diagnose patients and monitor remission and relapse of disease [7]. In case of multiple asymptomatic myeloma, β-2M level is an independent predictor of disease progression [8]. β-2M is considered to be a prognostic factor in MM beside serum albumin level, haemoglobin levels, creatinine level, high levels of serum calcium, C-reactive protein and Interleukin-6 [3,9,12,13,15,16].

## Conclusions

In this study, β-2M was directly correlated with creatinine, hypercalcemia, the percentage of bone marrow plasma cells, hyperproteinemia, monoclonal gradient, immunoglobulin G and inversely correlated with haemoglobin and low serum albumin, these correlations being statistically significant.

Median survival was of 48 months in the case of patients having β-2M < 3.5 mg/l, 43 months in the case of those having β-2M between 3.5mg/l and 5.55 mg/l and 20 months at patients having β-2M > 5.5 mg/l. The complete response to chemotherapy at patients with β-2M < 5.5 mg/l was better than those with β-2M > 5.5 mg/l. Patients with β-2M > 5.5 mg/l did not respond to therapy in greater proportion (30.43%) as compared to patients with β-2M < 5.5mg/l (4.76%). Median survival at patients with complete response to chemotherapy with β-2M > 5.5 mg/l was of 56 months while at those without response to chemotherapy being 4 months.

The high level of β-2M is a negative prognostic factor in the evolution of MM patients, adversely influencing therapeutic response rates and reducing the survival of patients with MM.

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