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IMPACT OF INITIAL RENAL INVOLVEMENT AND BENCE JONES PROTEINS IN THE URINE ON OVERALL SURVIVAL OF PATIENTS WITH MULTIPLE MYELOMA

Svetlana Krstevska Balkanov[1], Sanja Trajkova[1], Aleksandra Pivkova-Veljanovska[1], Dejan Spasovski[2], Nevenka Ridova[1], Goce Kalcev[3], Irina Panovska Stavridis[1]
[1]University Clinic for Hematology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia,
[2]University Clinic for Rheumatology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia,
[3]University of Cagliari, Cagliari, Italy

Abstract

Multiple myeloma (MM) is a cancer of plasma cells with a frequency of around 50 cases per million population (pmp)/year. This retrospective study was conducted at the University Clinic for Hematology in Skopje, North Macedonia, in the period between January 2009 and December 2019.

The cohort group was consisted of 296 recently diagnosed patients with MM. According to the results of our study, in 47% of patients who did not have renal involvement (RI), the survival rate was more than 60 months. On the other side, the survival percentage in those patients who had ARI (acute renal impairment) was 9% and in those who had CRI (chronic renal impairment) only 10%.

Forty percent of patients with a negative Bence Jones proteinuria survived more than 60 months. Besides, only 20% of patients with a positive Bence Jones proteinuria survived more than 60 months. Nowadays, bortezomib is generally used as a first-line drug in the treatment of MM in patients with serious RI. In conclusion, there are various research questions that can differentiate the treatment of patients with MM and RI in the near future.

Keywords: multiple myeloma, overall survival, renal involvement, BJP, impact.

Introduction

Multiple myeloma (MM) is a cancer of plasma cells with a frequency of around 50 cases per million population (pmp)/year [1].

The prevalence is higher in African-Americans than in Caucasians, and a complementary ethnic pattern is also acclaimed in the UK. MM is more frequent in males (56%) than in females (44%), with a male-to-female proportion of 6:5. Globally, it is the 23rd most common cancer [2, 3, 4].

In 50% of MM patients at the moment of diagnosis, renal impairment (RI) is discovered [5].

Up to 10% have a severe form of acute kidney injury (AKI) with an urgent need of dialysis treatment. The appearance of critical AKI is associated with an elevated risk of early mortality [6, 7].

In the immense majority of the cases, these deficient outcomes are also linked with a collapse to recover autonomous renal function. Up to 90% of these patients are secondary to myeloma cast nephropathy (MCN) [5].

Additionally, this condition is caused by high levels of immunoglobulin free light chain (FLC).

Overall, for revealing RI in clinical development and clinical intervention studies, several definitions have been applied. CRAB criteria (elevated calcium level, renal insufficiency, anemia and bone lesions) were popularized in 2003 with the intention to standardize the definition of end-organ suffering related to symptomatic MM. A creatinine level of >173 μmol/l (or >2 mg/dl) in the serum was the cut-off for RI [8].

Subsequently, the insufficiency of standardization in description of renal function in MM patients is a key shortage. Transforming serum creatinine into a considered glomerular filtration rate (eGFR) clarifies the potential for mistakes. The establishment of novel therapies has probably provided reports of greater survival outcomes for people with MM and serious kidney disease (marked as an estimated glomerular filtration rate [eGFR] at appearance of <30 ml/min/1.73 m2) [9].

Regarding complete survival, Bence Jones proteins (BJP) serve also as a crucial component, as well as a biomarker in urine for MM. The two different identified classes of these proteins are also known as kappa and lambda.

They are considered cornerstones with specific diagnostic importance in the context of target organ manifestations such as kidney failure, lytic bone lesions, anemia, or large numbers of plasma cells in the bone marrow of patients [10, 11].

The aim of this study was to report the role and impact of initial renal involvement and elevated levels of Bence Jones proteins on overall survival in patients with multiple myeloma.

Materials and methods

This retrospective study was conducted at the University Clinic for Hematology in Skopje, North Macedonia, in the period between January 2009 and December 2019. The cohort group was consisted of 296 recently diagnosed patients with MM. There were 146 (49.3%) female and 150 (50.7%) male patients, at the age ranging from 31 to 88 years (mean age 62 years). The diagnostic criteria of MM were established on the International Myeloma Working Group (IMWG) [12].

Patients were separated into different treatment groups after the staging of the disease (by IMWG), age, comorbidity status, and renal impairment. Patients younger than 65 years, in the absence of comorbidities, suitable for autologous peripheral blood stem cells (PBSCT), were treated with Cyclophosphamide-Thalidomide-Dexamethasone (CyThalDex) protocol split into two daily doses that were maintained until complete remission.

Patients over 65 years of age, unfit for more aggressive treatment options like PBSCT with comorbidities and renal failure, were treated with Melphalan-Prednisone-Thalidomide (MPT) protocol. The third group of patients was treated without new immunomodulators such as thalidomide, but alternatively, a salvage therapy was given consisting of chemotherapy and corticosteroids.

A written informed consent was obtained from all patients before starting the study. All medical history data were taken from the patient record database at the University Clinic for Hematology in Skopje.

Statistical analysis

Statistical analysis was made using the SPSS software, version 22. We used the Kaplan-Mayer survival curves (cumulative proportion surviving). The following survival analyses were done in this study: percentiles of survival analysis (comparison of two samples), Log Ranktest (comparison of multiple samples) and Chi-square (Descriptive statistics - median overall survival (OS)).

Results

According to the results, kidney involvement was not observed in 74.3% of patients with multiple myeloma. Acute renal impairment (ARI) was present in 13.2% and chronic renal impairment (CRI) in 12.5% of the overall number of patients with multiple myeloma (Table 1).

Table 1. Distribution of MM patients according to the initial renal involvement.

Kidney involvement	Number	%
ARI (acute renal impairment)	39	13.2
Without kidney involvement	220	74.3
CRI (chronic renal impairment)	37	12.5
Total	296	100.0

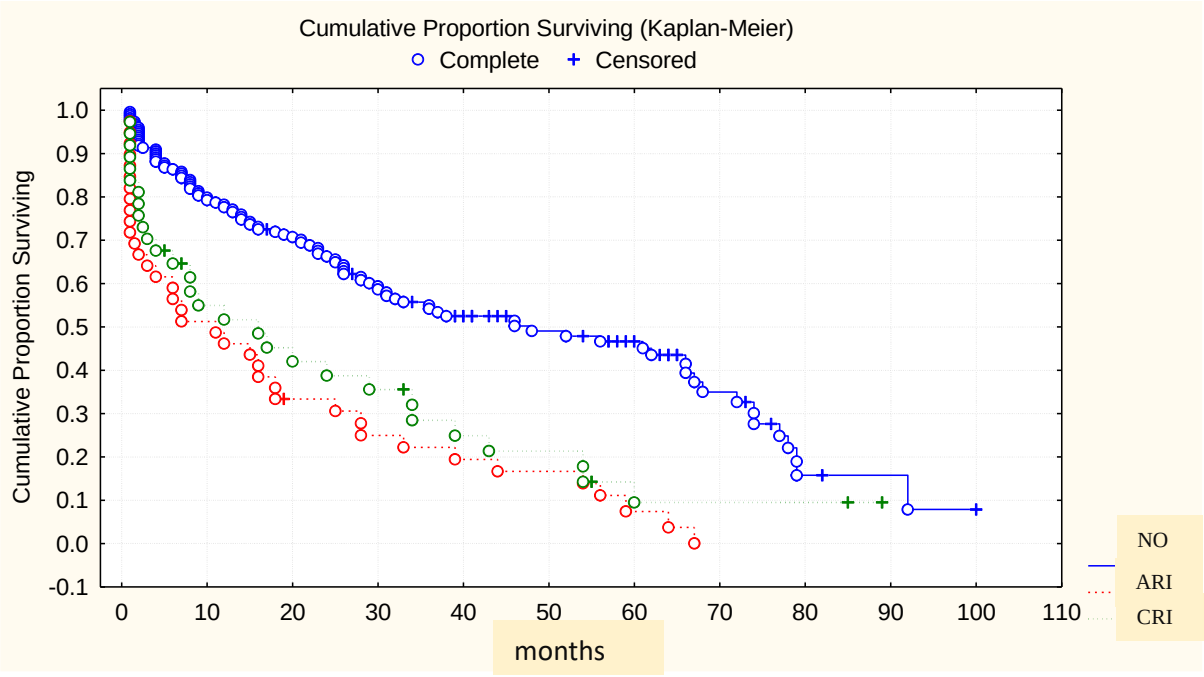

Figure 1. Overview of overall survival in MM patients according to the initial renal involvement.

In the 47% of patients who did not have renal involvement, the survival rate was more than 60 months. On the other side, the survival percentage in those patients who had ARI (acute renal impairment) was 9%, and in those who had CRI (chronic renal impairment) only 10%.

The average overall survival time in the group with no kidney involvement was 47.8 months, together with the median overall survival (OS) about 48 months.

The average overall survival time in the group of ARI patients was 19.5 months and the median survival time of 11 months.

Moreover, the average overall survival time registered in the group of CRI patients was 25.8 months, along with the OS of 16 months.

According to Chi-square ($p = 0.00000$), the difference between patients without initial renal impairment compared to patients with ARI and CRI showed that survival in the first group of patients was statistically significant (Figure 1).

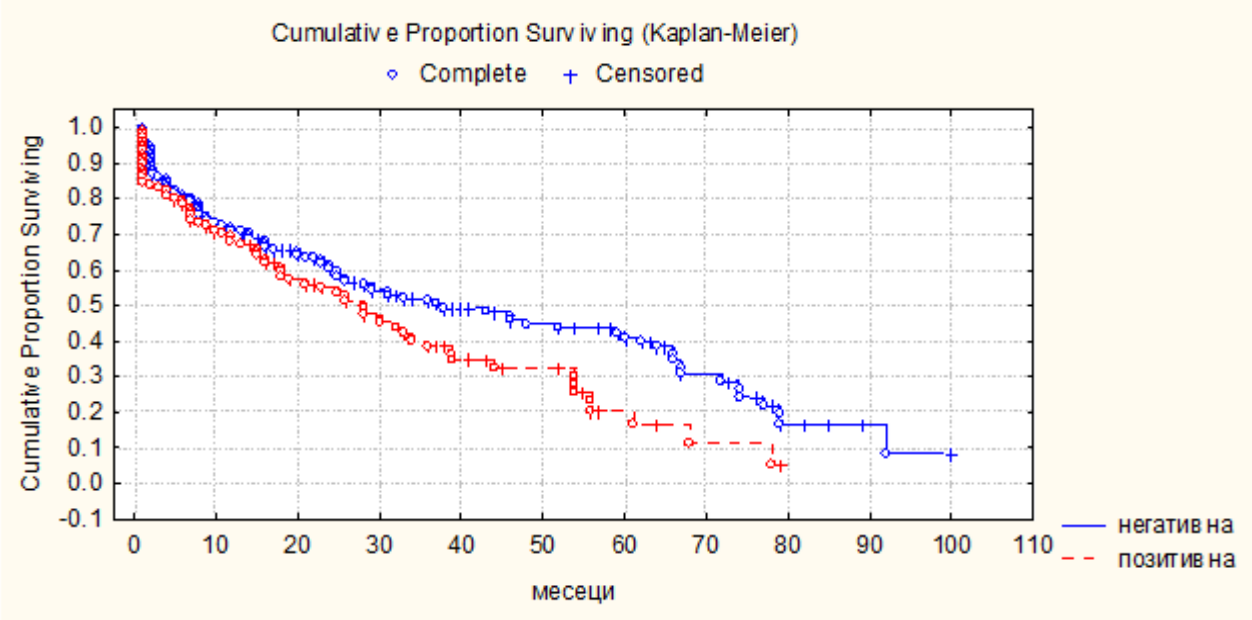

Figure 2. Overview of overall survival in MM patients according to Bence Jones proteins in urine

Forty percent of patients with a negative Bence Jones proteinuria survived more than 60 months. Besides, only 20% of patients with a positive Bence Jones proteinuria survived more than 60 months.

According to the Log-Rank test (p = 0.02512), the difference between positive and negative Bence Jones proteins in urine in relation to the overall survival in patients was statistically significant. Additionally, in the group of patients with negative Bence Jones protein in the urine, the median survival time was 37.3 months, and in the group with positive Bence Jones protein in the urine was 28 months (Figure 2).

Discussion

In the last decade, the development of multiple myeloma as a hematological disease is evident, starting from its biological roots, towards therapy and overall outcome [13].

In the near future, MM will no longer be considered as a single clinical entity, but a group of clinical entities, similar and close, but at the same time different in terms of the subtype and the approach of the clinicians who will guide the management. Renal involvement is one of the main predictors of shortened survival in MM subjects [14].

Hence, the urgent need for early recognition, emergency treatment with hemodialysis sessions, which according to our clinical experience have proven to be vital for the survival of patients, if implemented in a timely and adequate manner. Introducing early intervention leads to a reversible renal impairment, thus it is important to identify these patients rapidly and treat them algorithmically [15].

Dialysis has a crucial effect on the prognosis of MM. A median survival of 10.2 months was noticed in a single-centre study, where 82% of patients obtained dialysis at presentation; only 17% afterwards recuperated independent renal function.

These patients had a remarkably better OS in comparison with those who remained dialysis supported [16].

Single-centre studies have described better renal recovery rates of around 60% in patients who need dialysis, and an advancement in survival [17].

These reports have not yet been established in major prospective multicentre studies. The link of MM with dehydration, infection, hypercalcemia and bone pain advance to prescription of non-steroidal anti-inflammatory drugs [18].

Nonetheless, AKI in MM is a medical urgency. A satisfactory management comprises early institution of anti-myeloma therapy together with a good supportive care. Novel agents are related to awesome disease response.

Nowadays, bortezomib is generally used as a first-line drug in the treatment of MM in patients with serious RI [19].

Increased hemodialysis using high cut-off dialysers is more successful for extracorporeal removal of FLC than plasma exchange [20].

Also, high-dose chemotherapy along with autologous stem cell transplantation play a role in patients with severe RI, but prudent patient selection is required.

The effectiveness of novel treatments (bortezomib, carfilzomib, thalidomide, and lenalidomide) has principally been accepted in Western countries. Bortezomib and dexamethasone are the present level of care for MM in the West [21].

The withdrawal of FLC by high-cut-off hemodialysis is under estimation [22].

Studies in this area are not yet managed in China. In China, current treatments, including bortezomib, are broadly used than before, followed by satisfactory results [23].

However, RCT studies are still required in this direction to validate the efficacy and welfare of the novel treatments. Late perspectives of chemotherapy have led to a preferable overall survival (OS). Also, for patients who need dialysis, increased recovery rates of autonomous renal function are being reported [24].

Meanwhile, Ludwig *et al*. revealed shift of renal failure in five of eight patients, compromised five hemodialysis patients, who were treated with the bortezomib-based method [25].

Roussou *et al*. reported reversal of renal collapse in 40% of patients with MM who were on a bortezomib-based treatment pattern [26].

These data are in sharp distinction to historical data that revealed a poor renal recovery rate in dialysis-dependent patients with MM managed with regular chemotherapeutic agents.

Despite this, it is well-known that more than 60% of patients with classical myeloma have BJP in their urine [27].

According to the results of our study, the impact of Bence Jones proteinuria on the overall survival time was statistically significant. In those patients who did not have this type of proteinuria detected, the survival was longer. These results significantly open new horizons for novel diagnostic and treatment options.

Conclusion

In conclusion, there are various research questions that can differentiate the treatment of patients with MM and RI in the near future.

One of them is superior interpretation of the relationship between FLC level and renal function at diagnosis. Finally, patients with serious RI are often excluded from major intervention studies. Subsequently, future studies need to reach this fact as a step in the process of improving the evidence base of novel and next-generation drugs.

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