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Acta Haematologica Polonica

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DOI: 10.5603/ahp.94437

Article type: Original research article

Submitted: 2023-02-27

Accepted: 2023-06-04

Published online: 2023-10-30

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Early mortality, kidney failure, and venous thromboembolism in patients with multiple myeloma: a single-center analysis

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Abstract

The use of novel drugs with a different mechanism of action in the treatment of multiple myeloma (MM) has led to an improvement in survival rates, with an increase in median overall survival (OS) from 3-4 years to 5-7 years over the past 10 years. Still, it is estimated that 25% of patients die within less than 2 years from diagnosis. The objectives were to assess early mortality, the prevalence of kidney failure, venous thromboembolism (VTE), and to assess OS in patients with MM. A retrospective analysis of clinical and laboratory parameters in 413 patients with MM treated between 2006 and 2017. The early mortality rate in the study group was 13% (57 of the 413 patients). Mortality rates were higher in men [odds ratio (OR) = 1.4] ($p = 0.015$), patients with kidney failure (OR = 9.1) ($p = 0.001$), and patients with significant proteinuria and immunoglobulin A secretion (OR = 1.3). Early mortality was not associated with age, lactate dehydrogenase levels, or hemoglobin levels at diagnosis. Patients with kidney failure at diagnosis of MM had lower total protein levels ($p < 0.001$) and higher proteinuria levels ($p < 0.001$) than the remaining patients. The 5-year OS in patients with kidney failure was 20% vs. 50% in those without kidney failure ($p < 0.001$). VTE was reported in 38 patients (10.7%). There was no association between VTE and the patient's age, kidney failure, urinary protein levels, type of monoclonal protein, stage of MM according to the International Staging System, or type of

induction therapy. The median OS in the study group was 4.08 years. There was no correlation between VTE and OS in patients undergoing autologous hematopoietic stem cell transplantation.
Key words: early mortality, kidney failure, venous thromboembolism, overall survival, multiple myeloma

Introduction

Multiple myeloma (MM) remains an incurable disease, although novel drugs with a different mechanism of action have considerably improved survival rates. Over the past 10 years, median overall survival (OS) has increased from 3-4 years to 5-7 years. Nevertheless, it is estimated that 25% of patients die within less than 2 years from diagnosis. In 50% to 70% of patients, median survival is 5 years or longer, depending on response to treatment, treatment tolerance, and the possibility of using high-dose chemotherapy with autologous hematopoietic stem cell transplantation [1].

The rates of early mortality (<6 months from diagnosis) range from 10% to 14% and still constitute a significant challenge in clinical practice. Risk factors for early mortality include the patient's age, comorbidities, cancer stage, type of treatment, and biological characteristics of the disease. The identification of risk factors for early death might help reduce mortality rates and improve long-term outcomes of patients with MM [2, 3].

Kidney failure occurs in 50% of patients with MM and is one of the most significant predictors of lower survival. However, the median survival of patients with kidney disease in whom kidney function improved after treatment is similar to the median survival of patients with normal creatinine levels and estimated glomerular filtration rate at baseline. Bortezomib remains the first-line drug for the treatment of patients with MM and kidney failure. However, the use of immunomodulatory drugs (IMIDs) with dose reductions depending on creatinine clearance or the use of monoclonal antibodies (anti-CD38, anti-BCMA, and anti-SLAMF7) without dose adjustments may also be beneficial in this population [4-6].

Coagulation dysfunction in patients with MM have a complex pathogenesis. They develop due to plasma factors and platelet cell dysfunction, manifesting both as bleeding or thromboembolic complications. Numerous factors increase the

prothrombotic potential of plasma cells, including enhanced factor VII and von Willebrand factor activity, high P-selectin and fibrinogen levels, hyperfibrinolysis, acquired protein C resistance, reduced protein S levels, increased tissue factor and vascular endothelial growth factor expression, and increased thrombin formation and thrombin-activatable fibrinolysis inhibitor activity.

Risk factors for thrombosis are as follows: hyperviscosity syndrome; kidney failure; increased C-reactive protein levels; changes in the rheological properties of blood due to the presence of monoclonal protein; hypercalcemia; polychemotherapy regimens; treatment with IMIDs, anthracyclines, corticosteroids, or recombinant erythropoietin; age; immobilization; kidney failure; active infection; genetic predisposition; comorbidities; and previous surgery [7].

The lowest risk of thrombosis was shown for monotherapy with IMIDs (<5%). The risk is higher in patients receiving IMIDs in combination with high-dose dexamethasone and ranges from 11.5% to 26% [7]. The addition of doxorubicin increases the risk of thrombosis even up to 58% [7]. Zangari et al [8] showed that the risk of thromboembolic complications is lower in patients treated with IMIDs and bortezomib vs patients treated with IMIDs alone. They suggested that bortezomib may have antihemostatic effects, thus reducing the high prothrombotic potential of IMIDs. This indicates that newly diagnosed patients referred for a high-dose chemotherapy regimen with bortezomib and IMIDs as induction therapy can benefit not only from the high probability of achieving response to treatment but also from a lower risk of thrombosis [8].

Objectives

The objectives of this study were to assess the rates of early mortality (<6 months after diagnosis) as well as risk factors for early mortality in patients with MM, prevalence of kidney failure and its effect on survival, prevalence of venous thromboembolism (VTE) and its association with selected parameters such as age, cancer stage according to the International Staging System, monoclonal protein class, and type of treatment, and assess OS in patients with MM.

Material and methods

Characteristics of the study group

This retrospective study included 413 consecutive patients with MM treated at the Department of Hematology in Rydygier Hospital in Kraków, Poland, between 2006 and 2017. The study group included 234 women (56.7%) and 179 men (43.3%) with a mean age of 66.9 years (27-89 years). All patients underwent diagnostic tests for MM. Moreover, cancer stage and prognostic factors were assessed. Patients received causative treatment as well as supportive therapies such as intravenous bisphosphonates, blood product transfusions, erythropoietin, pain medications, and clinical psychological counseling.

Clinical and laboratory parameters as well as associations assessed in the study

The cause of death and early mortality (defined as death within <6 months from diagnosis) using a logistic regression model.

Kidney failure at diagnosis defined as a creatinine level higher than 177 μmol/L or creatinine clearance lower than 40 ml/min/m^2 according to 2014 International Myeloma Working Group criteria. Associations between kidney failure and total protein and urinary monoclonal protein levels at diagnosis were assessed. In addition, the association between kidney failure at diagnosis and OS was assessed.

Venous thromboembolism diagnosed on the basis of clinical symptoms confirmed by compression ultrasound or computed tomography angiography.

OS rates (OS defined as time from diagnosis to death or lost to follow-up) and time to progression (defined as time from the first and subsequent treatment lines to disease progression).

Statistical analysis

Qualitative variables such as selected laboratory parameters were presented as mean and SD, median, and minimum-maximum values. Variables were compared between subgroups divided according to risk, treatment, or selected clinical parameters (such as disease severity) using the nonparametric Mann-Whitney test for comparisons between 2 variables and the Wilcoxon test for comparisons between more than 2 variables.

Ranked or qualitative variables were presented as number and percentage of patients. Survival analysis was used to compare OS depending on selected risk factors, type of treatment, treatment outcomes after each line of chemotherapy, and selected clinical parameters. The independent χ^2 test was used in this subgroup to assess OS depending on selected factors as well as to assess the effect of selected risk factors on

OS shorter or longer than 5 years. The Kaplan–Meier method was used to assess survival curves.

Results with a *p* value of 0.05 or lower were considered significant. Statistical analysis was conducted using Statistica 13 PL (StatSoft, Kraków, Poland).

Results

Causes of early death

In our study, death was reported in 204 of the 413 patients, including 57 early deaths (27.9%). The most common causes of death were infectious complications, progression of primary disease, and multi-organ failure. The early mortality rate in the study group was 13% (57 of the 413 patients). Mortality rates were higher in men [odds ratio (OR) = 1.4] ($p = 0.015$), patients with kidney failure ($p = 0.001$), and patients with significant proteinuria and immunoglobulin A secretion (OR = 1.3) (Figure 1).

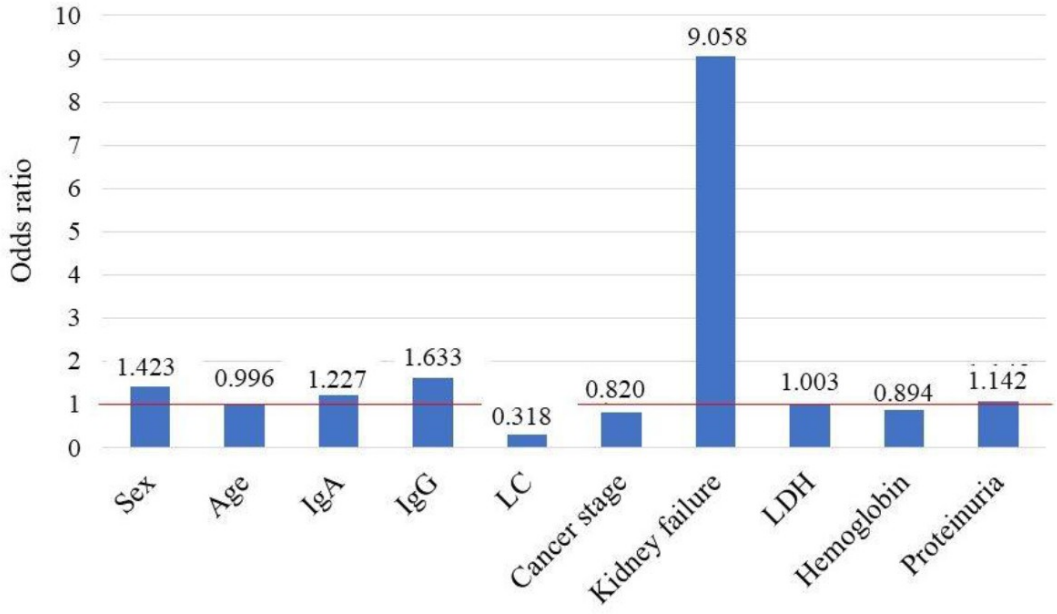

Figure 1. Odds ratio in the logistic regression model for predicting early mortality: IgA — immunoglobulin A; IgG — immunoglobulin G; LC —light chains; LDH — lactate dehydrogenase

The logistic regression analysis of ORs showed that kidney failure was a significant predictor of early death ($p = 0.004$). Kidney failure was associated with a 9-fold higher risk of early death (OR = 9.1) (Figure 1).

Early mortality was not associated with the patient's age, lactate dehydrogenase levels, or hemoglobin levels at diagnosis (Figure 1).

Kidney failure

Total protein levels in patients with kidney failure were higher than in patients without kidney failure ($p < 0.001$). The presence of kidney failure was associated with urinary protein levels ($p < 0.001$). Urinary protein levels lower than 1 g/L were noted in 69.73% of patients without kidney failure vs. 26.76% of patients with kidney failure. Despite higher proteinuria occurring in patients with kidney failure, there were not any amyloidosis cases (assessed by Red Kongo staining of bone marrow).

Kidney failure was associated with lower OS ($p < 0.001$). The 5-year OS rate in patients with kidney failure at diagnosis was 20% vs. 50% in those without kidney failure (Figure 2).

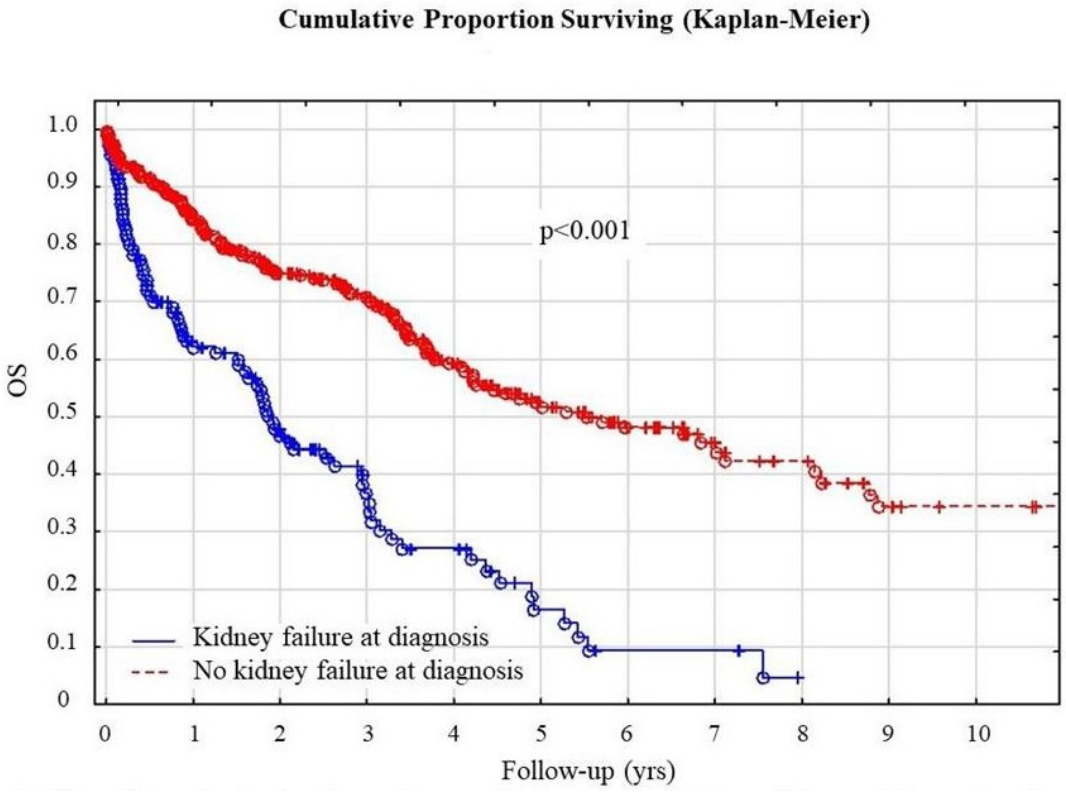

Figure 2. Overall survival rates depending on the presence of kidney failure at diagnosis of multiple myeloma

Venous thromboembolism

VTE was reported in 38 patients (10.7%). The presence of VTE was not associated with the patient's age, kidney failure, urinary protein levels, type of monoclonal protein, stage of MM according to the International Staging System, or the type of induction therapy (standard chemotherapy, bortezomib, thalidomide).

Overall survival

The median OS in the study group was 4.08 years (Figure 3).

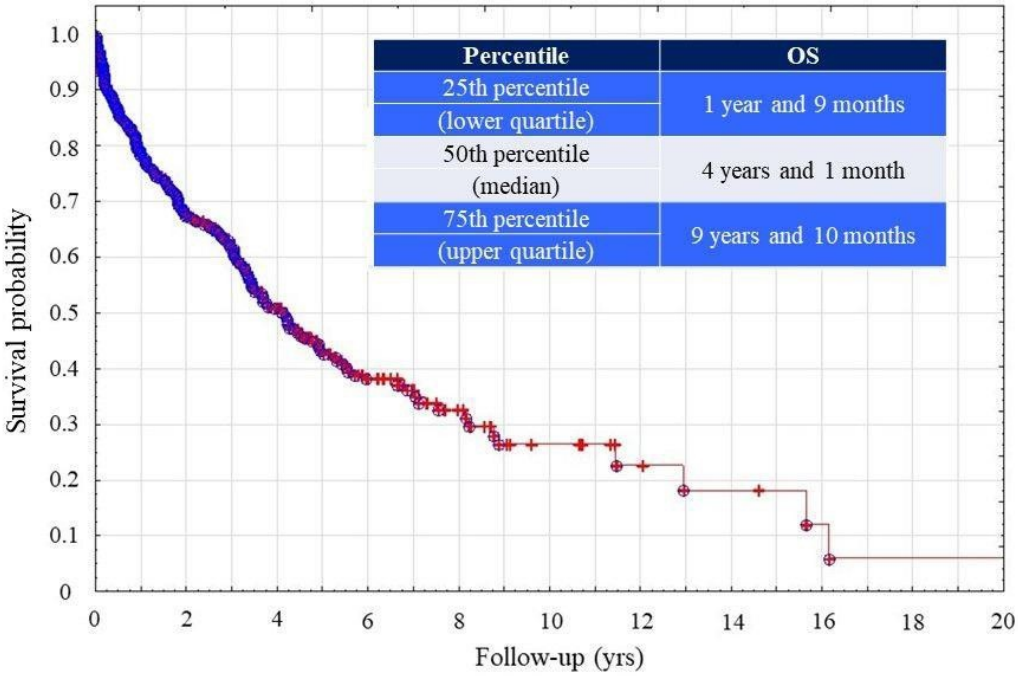

Figure 3. Overall survival in the whole study group

Discussion

In recent years, there have been significant advances in the treatment of MM due to the introduction of novel therapies, including IMIDs, proteosome inhibitors [1], as well as monoclonal antibodies, signaling pathways inhibitors and CAR T-cell therapy (immune therapy with genetically modified autologous T cells) [9].

Our study showed that kidney failure and significant proteinuria are associated with lower OS. Early mortality rates were significantly higher in men, patients with kidney failure, and significant proteinuria. These findings are in line with literature data [2, 3]. Of note, in our study, kidney failure was associated with a 9-fold higher risk of early death. Therefore, efforts should be made to restore normal kidney function, and patients should be referred for renal replacement therapy early enough to prevent further kidney damage during initial therapy and to increase the chances of improving kidney function. Infectious complications are the most common direct cause of death in MM. Therefore, prevention of bacterial infections (with sulfamethoxazole + trimethoprim or levofloxacine) as well as of viral infections is important [3].

Venous thromboembolism, either deep vein thrombosis or pulmonary embolism, is a common complication of cancer and is associated with higher mortality risk. Cancer-related risk factors for VTE include the type of cancer, chemotherapy, surgical treatment, use of central venous catheters, older age, or immobilization [10]. Approach to VTE treatment has been changing in recent years, and randomized clinical trials provide evidence to guide clinicians in making appropriate decisions on treatment [11]. The risk of VTE is 4- to 7-fold higher in patients with cancer vs those without cancer, with an annual incidence of up to 15% 12, 13]. In our patients, VTE was reported in 10.7% of cases. The risk of VTE in patients at an older age, with comorbidities, with more advanced disease, and those treated with IMIDs was similar to that in the remaining patients, which may be explained by the widespread and regular use of antiplatelet drugs (acetylsalicylic acid), low-molecular-weight heparin (LMWH), or non-vitamin K antagonist oral anticoagulants (NOACs; particularly edoxaban and rivaroxaban) for thrombosis treatment and prevention in these patients [11].

For many years, LMWH was the first-line treatment in cancer patients with VTE and low recurrence rate [relative risk (RR) 0.6], without an increased risk of major bleeding (RR 1.07), as compared with vitamin K antagonists. As for NOACs, they were initially used in patients without cancer, but two recent randomized clinical trials that compared the efficacy of NOACs vs LMWH in cancer-associated VTE have provided new evidence to support NOAC use in this population. Hukusai et al [14] randomized 1,050 patients with cancer to a group treated with oral edoxaban, a direct factor Xa inhibitor, or to a group treated with subcutaneous dalteparin for 6 to 12 months. Edoxaban was shown to be noninferor to dalteparin: the risk of VTE recurrence was lower by 3.4% hazard ratio [hazard ratio (HR) 0.71] and the risk of major bleeding was

higher by 2.9% (HR 1.77) in patients treated with edoxaban vs. those receiving dalteparin [14].

In the SELECT-D study including 406 patients with cancer, 6-month treatment with rivaroxaban, an oral factor Xa inhibitor, was compared with dalteparin. The cumulative risk of recurrent VTE was 4% in the rivaroxaban group vs 11% in the dalteparin group. The risk of major bleeding was 6% and 4%, respectively.

The use of NOACs seems to be an acceptable alternative to LMWH due to their efficacy, safety, and a convenient route of administration. In addition to the patient's preference, potential interactions between NOACs and anticancer drugs should be considered. Inhibitors and activators of P-glycoprotein and cytochrome p450 3A4 affect the metabolism of NOACs as well as their efficacy and safety profile. The most recent guidelines of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis recommend NOAC use in patients with cancer and newly diagnosed VTE, low bleeding risk, and no risk of drug-drug interactions. On the other hand, LMWH is recommended in patients at high bleeding risk, especially in the case of thrombocytopenia [15, 16].

Clinical trials in cancer patients confirmed the efficacy of NOACs for thromboprophylaxis [9]. It seems justified to use them as an alternative option for thrombosis prevention and treatment in patients with cancer, including those with MM.

Authors' contributions

MR — study conception and desing, manuscript writing. MagR, MarR — data collection and analysis, literature search and critical review**,** revision of manuscript et paper design, editorial preparation of the manuscript, language edition. All authors — critical revision and final approval.

Conflict of interest

None.

Financial support

None.

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