

ORIGINAL ARTICLE

Analysis of related risk factors and reversal value of renal injury in elderly patients with multiple myeloma

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Summary

Purpose: To study risk factors associated with renal injuries in elderly patients with multiple myeloma.

Methods: From January 2012 to January 2015 135 elderly patients with multiple myeloma who were treated in Xuzhou No.1 People's Hospital were enrolled in this study. Risk factors associated with their renal function, such as gender, serum levels of hemoglobin, uric acid, serum calcium and phosphorus, serum and urinary levels of β_2 microglobulin, diastolic blood pressure and light chain protein distribution were assessed before and after relative treatments.

Results: Compared with patients with normal renal function, the proportion of severe anemia, serum uric acid, calcium, and phosphorus levels were significantly higher in patients with abnormal renal function. Also, serum and urinary β_2 microglobulin levels and diastolic blood pressure were significantly higher in patients with abnormal renal function. Light chain protein of patients with abnormal renal function (mostly λ

protein), severe anemia, abnormally increased calcium and high diastolic blood pressure were independent risk factors in renal injuries. Blood urea nitrogen (BUN) and creatinine levels in both groups returned to normal after the anemia was corrected. Compared with the abnormal renal function group, one-year survival rate in the normal renal function group with myeloma was significantly higher.

Conclusion: Increased diastolic blood pressure, moderate and severe anemia as well as elevated level of serum calcium were independent risk factors for renal injuries in multiple myeloma. Blood pressure control (especially diastolic blood pressure) and correcting the anemia were proved to be effective means for reversing the disturbed renal function and ameliorating patients' quality of life.

Key words: kidney injury, multiple myeloma, relevant risk factors, reversibility

Introduction

Multiple myeloma, a common malignancy of plasma cells, is caused by the abnormal proliferation of a single plasma cell in the bone marrow. This often occurs with insidious onset and extremely complex clinical manifestations in the elderly patients [1-4]. Renal injury is the most common and the most serious complication and the main reason of poor prognosis [5,6].

Previous studies confirmed that about 50% of elderly patients with multiple myeloma suffered from renal injury. Renal proximal tubule, glomerular light chain deposits and renal proximal tu-

bule reabsorption disorders were the main manifestations, while the most common cause was the change of urinary monoclonal light chain [8,9]. The occurrence of renal injuries during the development of multiple myeloma remains the main obstacle to timely recovery. Prior studies [10,11] suggested that the median survival time of patients with multiple myeloma without renal injury was more than 2 years. This was reduced to 1 year in patients with kidney damage. For patients with reversed kidney damage, the median survival time was longer than 1 year. The number of

reports covering the effect of reversible factors in the prognosis of multiple myeloma patients with renal injury is quite limited [9-11].

In order to evaluate the effect of reversible factors on the renal function we investigated the risk factors associated with renal damage in elderly patients with multiple myeloma.

Subjects and methods

General information

From January 2012 to January 2015, 135 elderly patients with multiple myeloma, who were treated at Xuzhou No.1 People's Hospital, were enrolled in this study. There were 75 males and 50 females, aged from 60 to 81 years (mean 71.2 ± 2.3). Informed consent forms were signed by all patients and their relatives and were approved by Xuzhou No. 1 People's Hospital's ethics committee.

The diagnosis was made according to the diagnostic criteria of multiple myeloma of the Chinese Medical Association in 2010. Patients with other malignancies or mental diseases, severe heart and lung dysfunction as well as those with severe liver dysfunction, urinary system infection, solitary kidney complicated with urinary stones or who simply declined to sign the consent form were excluded from the study. Finally 103 cases with renal dysfunction and 32 cases with

normal renal function were included in the study and were divided in two groups according with the existence of renal function injuries.

Methods

Single factor analysis was conducted on all the related data obtained from all patients. These included gender, serum levels of hemoglobin, uric acid, serum calcium and phosphorus, as well as serum and urinary levels of β_2 microglobulin, diastolic blood pressure and light chain protein distribution (Table 1).

Risk factors associated with multiple myeloma were identified, and renal function was identified as independent variable. Multivariate logistic regression analysis was used to determine the independent risk factors of renal function injury. Antihypertensive drug therapy was used for patients with high blood pressure to improve the bone marrow hematopoietic function and the erythropoietin levels to correct anemia. For patients with hypercalcemia, we used calcium co receptor R-568 antagonist replacement treatment and diuretic therapy or dialysis therapy. All interventions lasted one month and patients were followed up for 12 months.

Observation index

Univariate and multivariate analyses were used to study the risk factors of renal function injuries in patients with multiple myeloma. Survival time according to the independent risk factors, as well as to the renal function and quality of life score were compared before and after intervention.

Table 1. Univariate analysis of abnormal renal function risk factors

| Risk factors | | Total number of cases | Abnormal renal function | χ^2 | p value |
|--|----------------------------|-----------------------|-------------------------|----------|---------|
| Gender | Male | 75 | 73 | 0.007 | 0.932 |
| | Female | 60 | 30 | | |
| Hemoglobin (g/L) | Normal or mild anemia | 35 | 13 | 40.052 | 0.000 |
| | Moderate and severe anemia | 100 | 90 | | |
| Uric acid ($\mu\text{mol/L}$) | ≥ 700 | 89 | 75 | 9.182 | 0.002 |
| | < 700 | 46 | 28 | | |
| Blood calcium (mmol/L) | Normal | 50 | 21 | 48.681 | 0.000 |
| | Abnormal increase | 85 | 82 | | |
| Blood phosphorus (mmol/L) | Normal | 48 | 29 | 10.385 | 0.001 |
| | Abnormal increase | 87 | 74 | | |
| Serum β_2 microglobulin ($\mu\text{g/ml}$) | Normal | 18 | 3 | 37.118 | 0.000 |
| | Abnormal increase | 117 | 100 | | |
| Urine β_2 microglobulin (ng/ml) | Normal | 20 | 3 | 44.879 | 0.000 |
| | Abnormal increase | 115 | 100 | | |
| Diastolic pressure (mmHg) | > 140 | 86 | 83 | 50.505 | 0.000 |
| | < 140 | 49 | 20 | | |
| Light chain protein type | λ | 69 | 65 | 23.039 | 0.000 |
| | κ | 66 | 38 | | |

Table 2. Multivariate logistic regression analysis of renal injury

| Factors | B value | S value | W value | p value |
|--|---------|---------|---------|---------|
| Moderate and severe anemia | 1.856 | 0.336 | 73.362 | 0.000 |
| Uric acid $\geq 700\mu\text{mol/L}$ | -0.521 | 0.189 | 9.268 | 0.113 |
| Abnormal increase of serum calcium | 1.773 | 0.296 | 56.669 | 0.000 |
| Abnormal increase of serum phosphorus | -0.089 | 0.096 | 3.552 | 0.076 |
| Abnormal increase of serum β_2 microglobulin | -0.115 | 0.103 | 4.569 | 0.081 |
| Abnormal increase of urine β_2 microglobulin | -0.326 | 0.118 | 8.625 | 0.103 |
| Diastolic blood pressure $\geq 140\text{mmHg}$ | 1.698 | 0.281 | 50.103 | 0.000 |
| Light chain protein type (λ protein) | -0.071 | 0.086 | 3.132 | 0.070 |

Table 3. Comparison of renal function before and after adjustment of blood calcium between the two groups

| Groups | | Blood urea nitrogen (mmol/L) | Serum creatinine ($\mu\text{mol/L}$) |
|-------------------------------|---------------------|------------------------------|--|
| Normal renal function group | Before intervention | 5.1 \pm 0.3 | 124.3 \pm 11.3 |
| | After intervention | 3.5 \pm 0.1* | 98.50 \pm 5.7* |
| Abnormal renal function group | Before intervention | 9.1 \pm 1.1 | 256.5 \pm 25.3 |
| | After intervention | 5.6 \pm 0.2* | 100.6 \pm 6.1* |

*Compared with values before intervention, $p < 0.05$

Appraising method

Normal range of renal function: BUN reference value of 1.8-6.8 mmol/L (Two acetyl-acetic acid method). Serum creatinine reference value: 79.6-132.6 $\mu\text{mol/L}$ for male patients and 70.7-106.1 $\mu\text{mol/L}$ for female patients.

The quality of life scores were assessed using Nottingham health survey questionnaire. Questionnaires were completed by researchers with more than 5 years of relevant research experience in strict accordance with the standards, including 6 aspects of energy, pain, emotion, sleep, social adaptation ability and physical function and were evaluated during treatment. The score range was from 0-100 points, where lower scores were associated with better quality of life.

Statistics

SPSS13.0 was used for statistical analyses. Measurement data were expressed by mean \pm standard deviation. The comparisons between two groups were analyzed using t-test. The comparison of enumeration data between groups was tested by χ^2 test. Univariate analysis of the related data was used. For data with statistical significance, non-conditional multivariate logistic regression analysis was implemented. Survival analysis was performed by Kaplan-Meier method and differences were assessed by log rank test. A p value < 0.05 indicated that the difference was statistically significant.

Results

Univariate analysis

The proportion of severe anemia, uric acid (≥ 700 mmol/L), abnormal increase of serum calcium and phosphorus, as well as serum and urinary

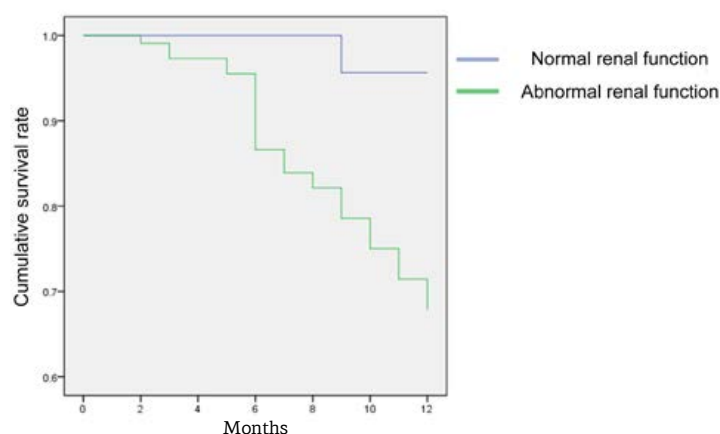


Figure 1. Comparison of 1-year survival rate of both groups ($p < 0.05$).

β_2 microglobulin, and diastolic blood pressure ($\geq 140\text{mmHg}$) in patients with abnormal renal function were significantly higher ($p < 0.05$) than those of patients with normal renal function. Additionally, light chain protein of abnormal renal function patients was predominantly λ protein ($p < 0.05$) (Table 1).

Multivariate logistic regression analysis

Based on the correlation factors of the univariate analysis in Table 1, logistic multivariate regression analysis results revealed that severe anemia, abnormal increase in calcium level and high diastolic blood pressure ($\geq 140\text{mmHg}$) were independent risk factors for multiple myeloma kidney injuries (Table 2).

Table 4. Comparison of renal function before and after blood pressure control between the two groups

| Groups | | Blood urea nitrogen (mmol/L) | Serum creatinine ($\mu\text{mol/L}$) |
|-------------------------------|---------------------|------------------------------|--|
| Normal renal function group | Before intervention | 5.1 \pm 0.3 | 124.3 \pm 11.3 |
| | After intervention | 3.6 \pm 0.1* | 86.9 \pm 5.9* |
| Abnormal renal function group | Before intervention | 9.1 \pm 1.1 | 256.5 \pm 25.3 |
| | After intervention | 5.5 \pm 0.3* | 120.3 \pm 5.3* |

*Compared with values before intervention, $p < 0.05$

Comparison of 1 year survival rate of both groups

In the normal renal function group, 31 patients (96.9%) survived after 1 year, while only 68.0% of patients in the abnormal renal function group survived after 1 year ($p < 0.05$; Figure 1).

Comparison of renal function of both groups before and after blood calcium adjustment

After the blood calcium level was adjusted within the normal range, BUN and creatinine levels in both groups returned to normal levels ($p < 0.05$) (Table 3).

Comparison of renal function of both groups before and after blood pressure control

After the blood pressure was brought under control, BUN and creatinine levels in both groups returned to normal, and these levels were lower than those recorded before treatment ($p < 0.05$) (Table 4).

Comparison of renal function of both groups before and after the correction of anemia

After the anemia was corrected, BUN and creatinine levels returned to normal. These levels were lower than the levels recorded before treatment ($p < 0.05$) (Table 5).

Comparison of the quality of life scores of both groups before and after intervention

In the normal renal function group no significant difference between the quality of life scores before and after intervention was detected ($p > 0.05$). Before the intervention, the quality of life score in the normal renal function group was higher than that of the abnormal renal function group ($p < 0.05$). Compared with the status before intervention, the quality of life score in the abnormal renal function group was significantly higher after the intervention ($p < 0.05$) (Table 6).

Discussion

Clinical manifestations of multiple myeloma are extremely diverse, which makes the diagnosis very difficult. More than 50% of patients are diagnosed with severe renal injuries, and after clinical diagnosis, nearly 40% of patients are usually treated for renal dysfunction or failure. It has been shown that severe renal dysfunction can dramatically affect patients' quality of life [12]. Results obtained from another study confirmed that renal injuries were one of the most significant causes of mortality in patients with multiple myeloma [13]. In order to improve the survival and patients' quality of life it is very important to control the

Table 5. Comparison of renal function before and after anemia correction between the two groups

| Groups | | Blood urea nitrogen (mmol/L) | Serum creatinine ($\mu\text{mol/L}$) |
|-------------------------------|---------------------|------------------------------|--|
| Normal renal function group | Before intervention | 5.1 \pm 0.3 | 124.3 \pm 11.3 |
| | After intervention | 4.1 \pm 0.2* | 70.9 \pm 6.3* |
| Abnormal renal function group | Before intervention | 9.1 \pm 1.1 | 256.5 \pm 25.3 |
| | After intervention | 5.8 \pm 0.4* | 115.6 \pm 4.8* |

*Compared with values before intervention, $p < 0.05$

Table 6. Comparison of the quality of life before and after intervention between the two groups

| Groups | Before intervention | After intervention |
|-------------------------------|---------------------|--------------------|
| Normal renal function group | 46.5 \pm 6.2 | 45.9 \pm 6.3 |
| Abnormal renal function group | 77.1 \pm 10.3 | 55.3 \pm 7.1 |
| <i>t</i> | 15.909 | 6.710 |
| <i>p</i> | 0.000 | 0.000 |

related risk factors and reverse renal function to normal or near-normal.

Usually patients with abnormal renal function suffer from severe anemia, higher serum uric acid, higher calcium and higher phosphorus levels. Also, serum and urinary β_2 microglobulin levels and diastolic blood pressure are significantly higher in patients with abnormal renal function. In these patients, the light chain protein of abnormal renal function is usually λ protein.

Using multivariate regression analysis we discovered that severe anemia, high calcium level and high diastolic blood pressure were independent risk factors for multiple myeloma kidney injury. In the normal renal function group, 31 patients (96.9%) survived after one year, while only 68.0% of patients in the abnormal renal function group survived after one year. It was confirmed that the survival of patients with multiple myeloma was seriously affected from renal function injuries. Moreover, our results suggested that in order to improve prognosis a normal renal function should be maintained.

Our results also showed that the abnormal increase in serum calcium level was an independent risk factors for renal injuries in multiple myeloma. We noticed that renal function improved significantly when the serum calcium levels were successfully controlled. The elevated levels of serum calcium in patients with multiple myeloma can easily lead to renal hemodynamics disorder. High calcium levels may enhance the ability of renal afferent arteriole contraction, resulting in the reduction of renal blood flow, the decrease of glomerular filtration rate and prerenal azotemia [14]. At the same time, high calcium level may lead to renal tubular filtration dysfunction and a reduction in the sensitivity of the collective tubes to the diuretic hormone. Both conditions can result in an increase in the filtration of ascending limb on sodium, potassium and chloride [15]. It can also lead to a decrease in renal concentration ability [15]. The consequent clinical manifestations are polyuria, diabetes insipidus, as well as a decline in the filtration of large molecular metabolites, such as BUN and creatinine, leading to abnormal renal function.

Additionally, long-term hypercalcemia may cause calcium deposition and calcium salt crystals formation in renal interstitium and tubules, and further damage of renal function. A meaningful improvement in the hypercalcemia problem can positively affect the renal function of multiple myeloma patients. It was shown that diastolic blood pressure was an independent risk factor

for the occurrence of renal injury in multiple myeloma. BUN and creatinine levels in both groups returned to normal after the patients' blood pressure was normalized. Several studies showed that hypertension is an independent risk factor for renal dysfunction [16-18]. In multiple myeloma patients with high diastolic blood pressure, the renal function was more likely to be impaired. The renal function was recovered after the blood pressure was effectively controlled. This could be explained by the fact that long periods of high blood pressure can lead to atherosclerosis of the renal artery and hence renal function damage. A reduction in renal blood flow may lead to a reduction of BUN and creatinine excretion barriers [19]. Hence, for patients with multiple myeloma, it is very important to have the blood pressure (especially the diastolic pressure) under control. Our results also showed that hemoglobin level was also an independent risk factor for renal function injury in multiple myeloma.

After the intervention, BUN and creatinine levels in the abnormal renal function group were back to normal, and were significantly lower than those before the correction of anemia. The infiltration of bone marrow by myeloma cells seriously affected the patients' hematopoietic function. The formation of red blood cells was significantly inhibited, and their lifespan was shortened. Results obtained from prior studies revealed that an increase in apoptosis rate induced by Fas ligand combined with tumor necrosis factor induced the dysmaturity of immature red cells [20]. In patients suffering from anemia, we usually observe an erythropoietin deficiency caused by renal damage which may lead to a significant drop in hemoglobin level. An improvement in bone marrow hematopoietic function and erythropoietin level can positively affect the patients' renal function.

In summary, the quality of life in patients with normal renal function was significantly better than in patients with abnormal renal function. We concluded that high diastolic blood pressure, moderate and severe anemia and high levels of serum calcium were the independent risk factors for renal injury in multiple myeloma patients. Blood pressure control (especially diastolic blood pressure), treatment of anemia and hypercalcemia were proved to be effective means to reverse the renal function and ameliorate patients' quality of life.

Conflict of interests

The authors declare no conflict of interests.

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