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BRIEF REPORT

Evaluation of Multiple Myeloma Patients Presenting with Renal Failure in a University Hospital in the Year 2010

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Abstract

Background: The aim of this cross-sectional study was to evaluate multiple myeloma patients presenting with renal failure in a University hospital. *Methods*: The records of all the patients diagnosed with multiple myeloma in the departments of hematology and nephrology at Gazi University Hospital between January 2010 and January 2011 were reviewed retrospectively. Renal failure was defined as a serum creatinine level of ≥2 mg/dL. Median age was 63 (range 37–80) years, with 13 male and 17 female patients. *Results*: Eight (26.7%) of the 30 patients had renal failure and 4 (50%) patients with renal failure required renal replacement therapy with hemodialysis after admission. Renal functions recovered in four (50%) of the eight patients after treatment. In one of the eight patients (12.5%) creatinine levels improved, but did not reach the level defined as reversal of renal failure. The renal functions of the three (37.5%) patients did not improve and they remained on chronic hemodialysis program during which one of them died due to a cerebrovascular accident and one other patient was lost due to follow-up. *Conclusion*: A substantial proportion of myeloma patients referred with renal failure might enjoy a disease-free survival and could be saved from chronic renal replacement therapy with prompt diagnosis and treatment in the era of new-generation anti-myeloma agents which provide fast and effective responses. Multiple myeloma should be considered in the differential diagnosis of acute renal failure even in the absence of hyperglobulinemia and hypercalcemia.

Keywords: multiple myeloma, renal failure, treatment, prognosis

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INTRODUCTION

Multiple myeloma (MM) comprises approximately 10% of the hematological malignancies[1,2] and has an annual incidence of 1.6–1.8% per 100,000 in Turkey.[3] Despite a relatively low incidence, MM causes serious morbidity in patients, one of which is renal failure. Renal failure is seen in 20–30% of the patients and has not decreased throughout the years despite the improved diagnostic modalities and medical facilities of today's world.[4–7] Renal failure usually occurs due to toxic effects of free light chains, synthesized in large amounts by plasma cells in MM patients. Light-chain disease, amyloidosis, and hypercalcemia are the less common causes of renal failure which might be precipitated by aggravating factors such as, dehydration, urinary tract infections, and/or nephrotoxic drugs.[8,9]

Renal failure is a well-established negative prognostic factor in MM patients associated with shorter overall survival (OS).[7,10] However, in the era of new anti-myeloma drugs such as bortezomib, immunomodulatory drugs, improvement in OS has been observed in patients with renal failure with the recovery of renal functions.[8,11] In addition to the positive impact of new agents, early mortalities have also decreased over years with the improvements in supportive care.[4,5] Since the myeloma patients presenting with renal failure, usually refer to the nephrology departments, a prompt diagnosis and treatment has a paramount role in the recovery of renal functions. The present study is designed to describe the annual rate and fate of the MM patients with renal failure referred to a nephrology clinic located in a university hospital in Ankara, Turkey.

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MATERIALS AND METHODS

The records of all the patients, who were diagnosed with MM, from January 2010 to January 2011 at Gazi University Hospital were reviewed retrospectively. The initial diagnostic work-up included complete blood count, serum albumin, globulin, lactate dehydrogenase, blood urea nitrogen, creatinine (Cr), uric acid, calcium (Ca) and serum electrolyte levels, serum and urine immunofixations, immunoglobulin levels, serum total and free light chains, bone marrow biopsy, β-2 microglobulin, creatinine clearance, and 24 h protein levels. The patients were staged according to Durie–Salmon[12] and International staging systems.[13] The response to treatment was assessed according to International Myeloma Working Group Criteria.[14] Renal failure was defined as a serum Cr level of ≥2 mg/dL. The glomerular filtration rate was calculated according to the modification of diet in renal disease formula from http://www.mdrd.com. The indications for initiation of dialysis in patients were uremia, hyperkalemia, metabolic acidosis, and fluid overload in the presence of renal failure. The reversibility of renal failure was accepted as a decrease of Cr to <1.5 mg/dL. The ratio of free light chains (*free* kappa/*free* lambda) was accepted as 0.26–1.65 in patients with normal renal function and 0.37–3.1 in patients with renal failure.[8] Amyloidosis was investigated in all renal and bone marrow biopsies.

Statistical evaluation was made by SPSS 11.5 program (SPSS Inc., Chicago, IL, USA). Data were presented as numbers and percentages or median and range, where appropriate.

RESULTS

The patient characteristics are summarized in Table 1. Median age was 63 (range, 37–80) years, with 13 male and 17 female patients. While 14 (46.8%) patients were stage IIIA, 7 (23.3%) were stage IIIB, 7 (23.3%) were stage IIA, 1 (3.3%) was stage IIB, and 1 (3.3%) patient was stage IA according to the Durie–Salmon staging system. Eighteen (60%) patients had lytic bone lesions and three (10%) had extramedullary disease. The laboratory results of the patients were as follows: median hemoglobin level was

Table 1. Patient characteristics.

	Patients without renal failure, *n* (%) *n* = 22	Patients with renal failure, *n* (%) *n* = 8	*p*-Value
Age (years), median (range)	63 (37–80)	62 (41–79)	0.801
Sex (F/M) (*n*)	14/8	3/5	0.298
Creatinine (mg/dL), median (range)	0.94 (0.52–1.72)	4.9 (2.02–12.9)	**0.00**
Creatinine clearance (mL/min), median (range)	71 (30–124)	11 (3–32)	**0.00**
<15	–	5 (62.5)	
15–29	–	1 (12.5)	
30–59	9 (40.9)	2 (25)	
60–89	10 (45.5)	–	
≥90	3 (13.6)	–	
Calcium (mg/dL) median (range)	9.45 (8.5–16.8)	12.3 (8.3–15.1)	0.78
≥11.5 mg/dL	2 (9.1)	5 (62.5)	
<11.5 mg/dL	20 (90.9)	3 (37.5)	
Hemoglobin (g/dL), median (range)	11 (6–16.6)	8.35 (7.26–10.5)	**0.024**
≥10.5 g/dL	14 (63.6)	1 (12.5)	
<10.5 g/dL	8 (36.4)	7 (87.5)	
Albumin (mg/dL), median (range)	3.4 (2.3–4.3)	3.4 (1.6–4.2)	0.662
Median β-2 microglobulin (mg/dL) (range)	4.9 (1.96–11.4)	16 (0.12–17.6)	0.055
ISS (data available in 23/29)			**0.036**
Stage I	4 (23.5)	–	
Stage II	6 (35.3)	–	
Stage III	7 (41.2)	6 (100)	
Myeloma subtype			0.597
IgG-kappa	11 (50)	4 (50)	
IgG-lambda	5 (22.7)	1 (12.5)	
IgA-kappa	1 (4.5)	–	
IgA-lambda	3 (13.6)	–	
IgM-lambda	1 (4.5)	–	
Free kappa	1 (4.5)	3 (37.5)	
Kappa/lambda (data available in 27/29 patients)			0.237
Normal	6 (30)	–	
Abnormal	14 (70)	8 (100)	
Bone marrow plasma cell ratio			0.447
>40	15 (68.2)	7 (87.5)	
≤40	7 (31.8)	1 (12.5)	

Note: The bold *p*-Values indicate that 0.00 should be <0.001.

10.25 g/dL (range 6–16.6), median Cr 1.08 mg/dL (range 0.52–12.9), median blood urea nitrogen 20 (range 6–88), median uric acid 6.85 (range 2.9–11.4), median Ca 9.65 mg/dL (range 8.3–16.8), median lactate dehydrogenase 172 U/L (range 114–281), median albumin 3.35 g/dL (range 1.6–4.3), median globulin 4.9 g/dL (range 0.54–14), median erythrocyte sedimentation rate 76 mm/h (range 7–130), median creatinine clearance 55 mL/min (range 3–124), median proteinuria 1322 mg/day (range 135–5516).

Eight (26.7%) of the 30 patients had renal failure and 4 (50%) of them required renal replacement therapy with hemodialysis after admission. Six (6.6%) of the 91 patients who were admitted to the nephrology department with acute renal failure were MM patients. Six (75%) of the eight patients with renal failure were initially admitted to the nephrology department. The median time from admission to commencing anti-myeloma treatment was 14 (range 3–24) days. Recovery of renal functions was observed in four (50%) patients after anti-myeloma treatment [bortezomib-cyclophosphamide-dexamethasone (VCD) (Patients 2, 4, and 6) and bortezomib-melphalan (Patient 3)]. Three of the four patients achieved sustained complete remission while one is in partial response and is still on chemotherapy (Table 3). One of the patients (12.5%) (Patient 5) had improved Cr levels; however, her Cr did not improve to the level defined as reversal of renal failure. She also is still on chemotherapy. The renal functions of two patients (Patients 1 and 7) showed no improvement with anti-myeloma treatment and they remained on hemodialysis. Patient 7 did not respond to induction chemotherapy and was started on a salvage regimen. Patient 1 developed pneumonia and required intensive care support after starting bortezomib-dexamethasone (VD). He required renal replacement therapy during his stay in the intensive care unit. Nearly 2 months after his discharge from the hospital, he died due to a cerebrovascular accident, while still on VD treatment without a significant response by then. One patient (Patient 8) was started VD treatment; however, she was lost to follow-up 2 months after commencing treatment while she was on hemodialysis (Tables 2 and 3).

All the patients were anemic, however, without any major symptoms of anemia. The major symptom was back pain in five (62.5%) of the eight patients and compression fracture was detected in all of the five patients. In these five patients, MM was suspected after the laboratory evaluation which showed renal failure and hypercalcemia due to widespread bone disease. Two patients (Patients 5 and 6) were diagnosed with MM after renal biopsy. The presentation of these two patients was with gastroenteritis; thus, renal failure was considered to be of prerenal origin. The absence of hypercalcemia and hyperglobulinemia and failure of renal functions to improve with rehydration prompted the nephrologists for a renal biopsy after which MM

Table 2. Clinical and laboratory features of the patients with renal failure.

	Age/sex	Myeloma type	Stage: Durie–Salmon/ISS	fκ/fλ	Cr (mg/dL)	CrCl (mL/min)	Proteinuria (mg/24 h)	Ca (mg/dL)	LDH (U/dL)	Hb (g/dL)	Alb (g/dL)	Amyloidosis	Symptoms	DOS	Department of first admission
Patient 1	59/M	IgG-kappa	IIIB/III	408	2.17	27	1254	14.3	194	7.7	2.2	Negative	Back pain, weight loss, polydipsia	2 months	Hematology
Patient 2	65/M	IgG-lambda	IIIB/III	0.0014	6.38	10	3820	12.7	281	7.9	4.2	Negative	Back pain	3 months	Nephrology
Patient 3	76/M	IgG-kappa	IIIB/III	445	2.02	33	1185	12	161	10	3.4	Negative	Back pain	4 months	Nephrology
Patient 4	55/M	IgG-kappa	IIIB/III	170	3.99	12	1054	14.5	120	8	1.6	Negative	Back pain	3 years	Internal medicine
Patient 5	72/F	Kappa	IIIB/III	192	3.74	12	2584	8.9	231	9.6	3.3	Negative	Gastroenteritis	2 days	Nephrology
Patient 6	41/F	IgG-kappa	IIIB/?	1231	12.9	4	2608	10.5	205	8.7	3.8	Negative	Gastroenteritis	1 week	Nephrology
Patient 7	56/M	Kappa	IIIB/III	1660	5.81	14	5516	15.1	174	10.5	3.5	Negative	Back pain	2 months	Nephrology
Patient 8	79/F	Kappa	IIIB/?	978	6.92	7	3261	8.34	217	7.26	3.1	Negative	Nausea, vomiting	1 months	Nephrology

Notes: Alb, albumin; Ca, calcium; Cr, creatinine; CrCl, creatinine clearance; DOS, duration of symptoms; fκ/fλ, free kappa/free lamda; Hb, hemoglobin; ISS, international staging system, LDH, lactate dehydrogenase.

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Table 3. Treatment data and the outcome of the patients with renal failure.

Patients	Treatment	Dialysis	Cr at admission (mg/dL)	Cr after treatment (mg/dL)	CrCl at admission (mL/min)	CrCl after treatment (mL/min)	Time from admission to the start of treatment	Disease response	Duration of disease response (months)	Outcome
1	VD	Yes	2.17	7.16	32	8	7 days	NA	NA	Died/on dialysis
2	VCD	No	6.38	1.29	9	56	21 days	CR	12	Alive/not on dialysis
3	V-mel	No	2.02	0.96	32	76	18 days	CR	15	Alive/not on dialysis
4	VCD	No	3.99	0.72	16	113	12 days	CR	15	Alive/not on dialysis
5	VCD	No	3.74	2.62	12	18	12 days	PR	6	Alive/not on dialysis
6	VCD	Yes	12.9	1.33	3	46	24 days	PR	5	Alive/not on dialysis
7	VCD	Yes	5.81	5.3	10	9	3 days	NR	NR	Alive/on dialysis
8	VD	Yes	6.92	?	7	?	17	NA	NA	Lost to follow-up/on dialysis

Notes: Cr, creatinine; CrCl, creatinine clearance; CR, complete remission; NA, not assessed; NR, no response; PR, partial remission; VD, bortezomib-dexamethasone; VCD, bortezomib-cyclophosphamide-dexamethasone; V-mel, bortezomib-melphalan.

was diagnosed. The remaining one patient had ongoing nausea and vomiting for the past 1 month which was followed by the deterioration of the renal functions. She was suspected of having MM, as she had anemia, high erythrocyte sedimentation rate, acute renal failure, hyperglobulinemia, and her immunofixation showed kappa-type monoclonal gammopathy.

DISCUSSION

MM is a disease characterized by the clonal proliferation of plasma cells in the bone marrow. The malignant cell clone secretes monoclonal intact immunoglobulins with two heavy and light chains along with free unassociated light chains. Immunoglobulin light chains are metabolized in the proximal tubuli of the kidney. The large amounts of free light chains which accumulate in blood can cause damage in various parts of the kidney such as nephron, glomeruli, tubuli, interstitium, and blood vessels.[8,9] The incidence of the renal failure in MM patients, ranging approximately between 20% and 40% depending on the definition of renal failure and the threshold Cr level, has remained the same over the years.[4–7] Cast nephropathy, the so-called myeloma kidney, is the most common kidney pathology in MM followed by light-chain deposition disease and amyloidosis.[11,15] Normally serum-free light chains (SFLC) are filtered through glomeruli into the proximal tubuli where they are reabsorbed and metabolized by the tubule cells. When SFLC overwhelm the capacity of proximal tubuli, they enter the distal tubuli where they bind to Tamm–Horsfall proteins and cause obstruction and reduction of the glomerular filtration and interstitial blood flow rate, all of which lead to interstitial nephritis from tubular rupture.[8,9] The typical clinical presentation of patients with cast nephropathy is acute renal failure which is aggravated by factors such as dehydration, hypercalcemia, acidosis, non-steroidal anti-inflammatory drugs, and furosemide.[8,9] Albeit the acute and disastrous presentation of the cast nephropathy, it is the most reversible among other renal myeloma lesions if treated early. In light-chain deposition disease, non-fibrillar monoclonal protein is deposited along the glomerular and tubular basement membrane in mesangium and vessel walls. The deposition causes glomerular sclerosis, clinically leading to nephrotic syndrome. Similarly, nephrotic syndrome is the prominent clinical feature in amyloidosis where there is deposition of light chains in beta-pleated sheet of fibrils mainly in the glomeruli.[8] Although we performed renal biopsy showing cast nephropathy in only two patients, probably others also had cast nephropathy. The onset was abrupt with deterioration of renal functions followed by rapid recovery with prompt treatment in five of them. One patient was lost to follow-up. The remaining two patients did neither respond to chemotherapy nor had a reduction in Cr levels and one of them died due to a cerebrovascular accident. It should be noted that all

the patients with renal failure had common aggravating factors such as hypercalcemia and/or dehydration.

There have been attempts to decrease the light-chain toxicity by means of plasmapheresis and dialysis in MM patients. Although plasma exchange has a role in patients with hyperviscosity, and provide some reduction in SFLC levels, its benefit with respect to reversal of renal functions could not be confirmed in prospective trials.[8,9,11,16] However, a new-generation dialyzer with larger pores (The Gambro HCO dialyzer) along with the new anti-myeloma agents offers a promising approach in reducing the SFLC, leading to faster and more efficient renal recovery.[8,11,16–18] We perform plasmapheresis in MM patients with hyperviscosity and use standard hemodialysis in patients requiring renal replacement therapy per institutional practice. Plasmapheresis was not required in the presented cohort as none of them had symptoms of hyperviscosity at presentation.

Considering the fact that survival of hemodialysis patients with MM is shorter than the patients with normal renal functions[8] and the reduction of early mortality and the prolonged OS with improved renal functions,[4–7] every effort should be exerted to improve renal functions. It is also noteworthy that two of the patients in the present series presented with renal failure followed by an attack of diarrhea, which we believe is due to decompensation of the borderline renal functions and underlies how important it is to keep myeloma patients well hydrated. In patients requiring hemodialysis, reversal of renal functions after the treatment is not satisfactory.[6–8] While in a group of 107 MM patients with renal failure 17% of the hemodialysis patients among 88 patients became free of dialysis,[6] none of the MM patients undergoing hemodialysis got rid of dialysis in a study conducted by Nordic Myeloma Group.[7] In our analysis, only one patient among four showed improvement in renal functions and eluded from hemodialysis.

Before the introduction of novel agents such as bortezomib and immunomodulatory drugs, the response to treatment was less impressive in MM patients with renal failure.[4,5] In recent years, bortezomib-based chemotherapies have been shown to improve renal functions in MM patients with renal failure, without causing increased toxicity despite no dose adjustment.[19,20] Bortezomib also decreases inflammation and interstitial fibrosis through inactivation of transcription factor NF-κB which is activated in renal tubular cells of patients with proteinuria.[8,9] Similar to bortezomib, high-dose dexamethasone was demonstrated to improve renal functions in MM[9,21] suggesting bortezomib combined with dexamethasone should be the frontline therapy for MM patients complicated with renal failure.[8] Our standard approach in MM patients with renal failure is induction with VD or VCD, and proceeding with high-dose melphalan and autologous stem cell transplantation (ASCT) after obtaining at least partial remission. Higher 100-day mortality and a shorter OS have been reported in MM patients with renal failure receiving ASCT in a large series of 678 patients from Mayo Clinic.[22] Notwithstanding, being on renal replacement therapy is not an obstacle to high-dose chemotherapy and ASCT.[8,23,24] Moreover, recovery from dialysis is possible particularly for patients with cast nephropathy who are on hemodialysis program for 6 months or less.[8,9] The role of allogenic stem cell transplantation has not been well established in myeloma patients on dialysis treatment yet.[8] VD, VCD, or bortezomib-melphalan was administered in our patients which resulted in reversal of renal functions in four (50%) and improvement in one (14%) of the eight patients. The reversibility of renal functions with chemotherapy was reported to vary between 26% and 73%.[4,7,8] It should be mentioned that the two patients who remained on renal replacement therapy did not respond to induction chemotherapy, while patients achieving complete remission had completely recovered renal functions, suggesting that failure to improve in renal functions might be due to more aggressive tumor biology. Also response to chemotherapy seems to be the main determinant factor in the reversibility of myeloma kidney.

In conclusion, despite improved diagnostic techniques, renal failure is the presenting clinical feature in about a quarter of MM patients and remains to be a serious cause of morbidity and mortality. Since the reversibility of renal failure with new-generation anti-myeloma agents is likely, renal failure as the presenting feature might not necessarily be a poor prognostic factor for MM. Considering the fact that prompt diagnosis and treatment is essential in the reversal of renal failure associated with MM and 71% of our myeloma patients with renal failure had referred to nephrology clinics, a high index of suspicion of the nephrologists is required for myeloma kidney even in the absence of hyperglobulinemia and hypercalcemia. Presence of anemia and back pain might be important clues for the diagnosis of MM. Patients with more aggressive tumor biology who fail to achieve complete response with bortezomib-containing regimens might remain to have a poor prognosis at least with respect to renal functions.

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