

RENAL STATUS OF MULTIPLE MYELOMA PATIENTS IN IBADAN, NIGERIA

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ABSTRACT

Introduction: The spectrum of clinical manifestation in multiple myeloma (MM) ranges from asymptomatic disease to severely debilitating state. Unexplained renal disease is an indication for the investigation of patients for MM. This study is a retrospective analysis of the renal profile of patients with multiple myeloma in relation to management strategy in our institution.

Methods: Medical records of 64 patients with multiple myeloma seen between 2000 and 2008 were retrospectively reviewed at an 850-bed tertiary hospital in South-Western Nigeria. The Mahn-Whitney test was used to compare laboratory features between patient with renal failure and those without renal failure. Subjects with serum creatinine $\geq 2\text{mg/dL}$ were regarded to have renal failure. Overall survival was calculated from diagnosis to death or lost to follow-up

Results: A total of forty three patients were eligible. The renal status was categorized into three according to serum creatinine level; those with normal serum creatinine level (0.5-1.5mg/dl) were 26 (60.5%), serum creatinine level ($>1.6-1.9\text{mg/dl}$), and creatinine level $\geq 2\text{mg/dl}$ were 3(7%) and 14(32.5%) respectively. Hyperuricaemia was observed in 6(42.9%) of MM patients with renal failure compared with 7(26.9%) of patient without renal failure ($p < 0.05$). Twenty-one percent of those with renal failure had hypercalcaemia. Thirty-six percent of the renal failure patients had haemodialysis. The average survival for all patients with renal failure was 18 months after diagnosis.

Conclusion: The outcome in patients with renal failure remained poor with early mortality despite supportive management. Hyperuricaemia and dehydration, given the hot climate might have worked in concert with other factors to worsen the renal status in these patients.

Keywords: renal, creatinine, myeloma, dehydration

INTRODUCTION

Multiple Myeloma (MM) is a malignant clonal proliferation of plasma cells, which are terminally differentiated B-cell. It is invariably accompanied by production of monoclonal (M) protein. The diagnosis is hinged on bone marrow plasmacytosis $>10\%$ or histological confirmation of plasmacytoma, a monoclonal protein in the serum and/or urine (except in non-secretory myeloma) and bone disease. Spectrum of clinical manifestation ranges from asymptomatic disease to severely debilitating state. The tumor, its product and the host response to it result in a number of clinical features including organ dysfunction. Clinical features are heterogeneous and include renal failure,

increased susceptibility to infection, anaemia, hypercalcaemia, occasionally neurological symptoms, vascular manifestation of hyperviscosity and clotting abnormality. The incidence of myeloma increases with advancing age. It is commonest among blacks¹, it accounts for 0.5% of all malignancies and 5.7% of haematological disorders in our hospital².

Kidney involvement is seen in up to 50% of cases³, and can be identified at presentation or during the course of the disease. Unexplained renal disease is an indication for the investigation of multiple myeloma. The pathology is heterogeneous with a variety of

pathogenetic mechanisms³, many factors contribute to this renal lesion, most frequent being deposition of monoclonal immunoglobulins or fragments with cast nephropathy^{3,4}. Tubular damage associated with the excretion of light chains is almost always present⁴. Renal status of MM patients is an important prognostic determinant, and this forms the basis for subdivision of Durie-Salmon staging into A and B. Thus the approach to management is often modified by the patient's renal status.

This aim of this study was to assess the renal profile of patients with multiple myeloma in relation to current management strategies in our institution.

MATERIALS AND METHOD

Medical records were retrospectively reviewed for all patients diagnosed as multiple myeloma in the Haematology department of a tertiary hospital in South-Western Nigeria between 2000 and 2008. Multiple myeloma was defined by at least 2 of the following-bone marrow with clonal plasma cells of at least 10% or histologic confirmation of a plasmacytoma; a monoclonal protein in the serum or urine (unless the patient has a nonsecretory myeloma); and end-organ damage evidenced by renal insufficiency, hypercalcemia, anemia, or lytic bone lesions (International Myeloma Working Group, 2003, Rajkumar & Kyle, 2005).

Forty three patients who met the diagnostic criteria and had complete data with regard to availability of serum creatinine, urea and electrolytes were included in the study. The presenting features and significant co-morbidity were recorded. All patients included in this study had bone marrow plasmacytosis greater than 30%. Clinical staging was determined according to the

Durie -Salmon system. Drug regimen, supportive care and outcome were recorded.

Renal status was categorized into normal, renal insufficiency and renal failure using results of serum creatinine. Normal renal status was defined by the hospital laboratory reference value of serum creatinine level between 0.5 and 1.5mg/dl. Renal insufficiency was defined as a serum creatinine level of 1.6–1.9 mg/dl while renal failure was defined as serum creatinine ≥ 2 mg/dl. In all the patients, diagnosis of renal disease was made at the time of investigating patient for MM. In line with the International Prognostic Index (IPI) hypoalbuminaemia was defined as serum albumin < 3.5 mg/l

A corrected calcium concentration = Serum calcium concentration + 0.02 (40 – serum albumin concentration) was calculated for each patient.

Statistical Analysis

The Kruskal Wallis test was used to compare the biochemical parameters of MM patients with renal failure and those without. The survival time was calculated as number of months from diagnosis to death or date of last follow-up. Survival rates were estimated using the Kaplan – Meier method while the long rank test was used to compare the survival rate between the two categories of MM patients (with and without renal failure). P-values less than 0.05 were considered statistically significant.

RESULTS

A total of forty-three patients consisting of 26(60.5%) males and 17(39.5%) females were studied. Their age ranged from 36 to 85 years with a median of 65 years. The urea level at presentation ranged from 10 to 390

| Parameter | Mean (SD) | | | p-value |
|-----------------------------|---------------------|---------------------|----------------------|---------|
| | Normal Renal Status | Renal insufficiency | Renal failure | |
| Total protein(g/l) | 9.06 (2.26) | 11.10 (2.75) | 9.16 (2.10) | 0.482 |
| Corrected calcium (mg/dl) | 10.16 (0.95) | 11.53 (1.09) | 10.16 (2.15) | 0.136 |
| Uric acid(mg/dl) | 5.07 (3.29) | 9.18 (8.28) | 5.95 (6.06) | 0.675 |
| PCV (%) | 25.64 (6.32) | 17.5 (6.36) | 21.08 (7.50) | 0.088 |
| WBC(/mm ³) | 5027.78 (1924.39) | 6300 | 5322.22(2976.48) | 0.757 |
| ESR(hr ⁻¹) | 92.11 (36.41) | 118.33 (22.55) | 107.46 (40.35) | 0.355 |
| Platelet(/mm ³) | 215788.9 (124176.8) | 120000 (113137.08) | 1597333.3 (108657.2) | 0.301 |
| Globulin(g/l) | 5.93 (2.24) | 8.70 (3.18) | 5.90 (1.59) | 0.224 |
| Albumin(g/l) | 1.32 (0.95) | 2.00 | 1.23 (1.01) | 0.227 |
| Urea(mg/dl) | 34.58 (18.11) | 98.00 (33.29) | 137.92 (85.43) | 0.000* |

Table 1: Laboratory features of MM Patients according to renal status

| Characteristic | Renal failure, N=14 n(%) | Without renal failure N=26 n(%) |
|---------------------|-----------------------------|------------------------------------|
| Osteolytic lesions | 11(78.6) | 20(76.9) |
| Hypercalcaemia | 5 (35.7) | 3 (11.5) |
| Hyperuricaemia | 6 (42.9) | 7(26.9) |
| Bence Jones Protein | 5(35.7) | 9(34.6) |
| Hypoalbuminaemia | 11(78.6) | 16(61.5) |

N = number of patients

Table 2: characteristics of MM patients with renal failure and without renal failure

mg/dl with a median value of 49mg/dl while creatinine had a range of 0.3 to 19.7 with a median of 1.5. Renal failure was observed in 14 patients (32.6%), 3 (7.0%) had renal insufficiency while 26(60.5%) had normal renal status.

protein and globulin, corrected serum calcium, uric acid, white blood cell count, erythrocyte sedimentation rate (ESR) tend to be higher in patients with renal insufficiency while the packed cell volume(PCV) and platelet were lower. According to Durie-Salmon staging, 13(92.8%) were stage 111. Figure 1 shows the frequency of renal failure among the patients. Younger patients were more likely than older adult to have renal failure. Bence Jones Protein was positive in the urine of 5(35.7%) patients with renal failure. Of the patients with renal failure, 4(28.6%) had Ig (immunoglobulin) G myeloma while 2(14.2%) had IgA and non-secretory myeloma respectively. The number of patients with radiological evidence of osteolytic lesion and other complications of the disease are as shown in Table 2. All patients received supportive treatment with hydration and blood transfusion as needed. The patients with abnormal blood urea level were not given biphosphonate. The chemotherapeutic regimen

| Treatments | Responders (%) | non responders(%) | Number of Patients (%) |
|--------------|----------------|-------------------|------------------------|
| M+P | 2 (33.3) | 2 (25) | 4 |
| VAD | 1 (16.7) | 3(37.5) | 4 |
| VAD/M+P | 3 (50) | 1(12.5) | 4 |
| No treatment | 0 (0) | 2 (25) | 2 |
| Total | 6 (100) | 8 (100) | 14 |

Table 3: Treatment response of patients with renal failure

Table 1 shows the mean laboratory features of the MM patients with renal failure and those without. Urea was significantly elevated in patients with renal failure ($p < 0.05$). Mean serum creatinine for patients with renal failure was 7.41mg/dl. The values for total serum

administered were melphalan and prednisolone (M + P), Vincristine, Adriamycin and Dexamethasone (VAD) and a hybrid of VAD/M+P. The hybrid combination was received by patients who did not have an initial favourable response to VAD. The response of patients

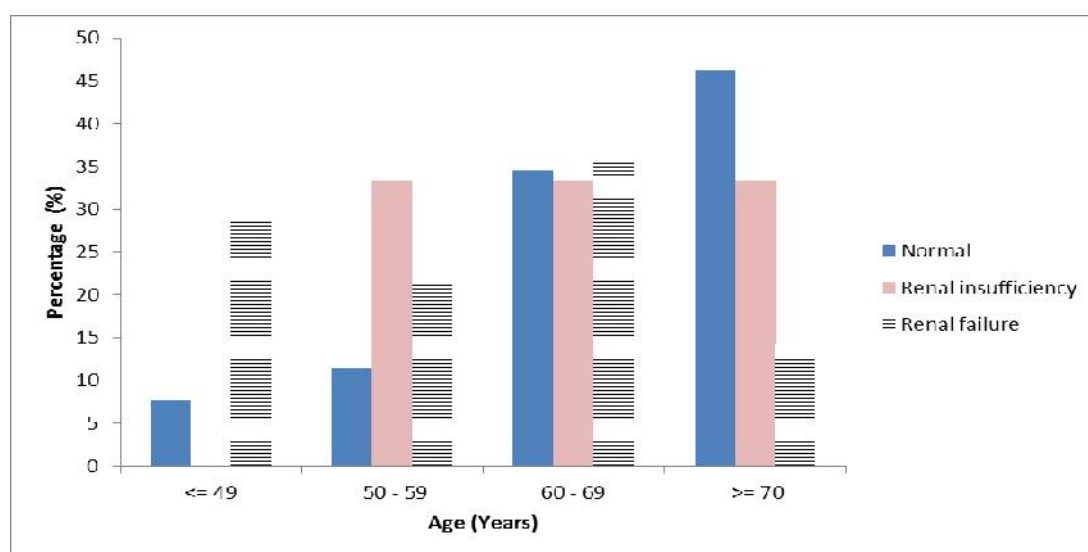


Figure 1: Distribution of MM patients with according to age group and renal status

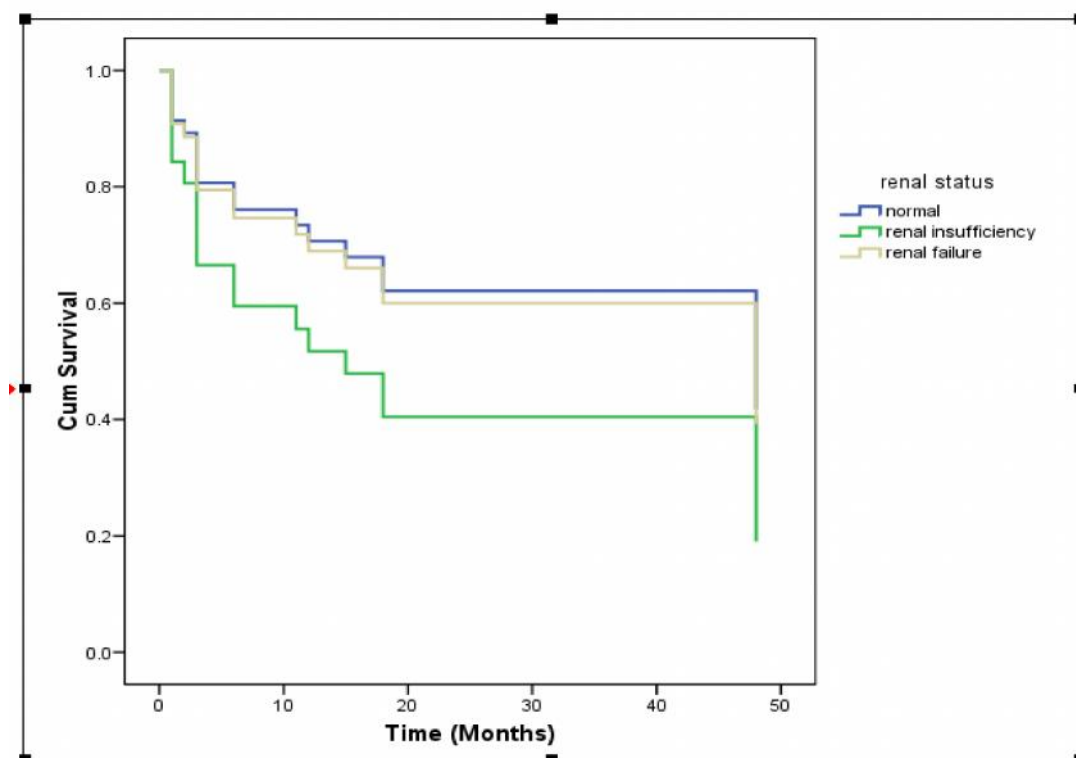


Figure 2: Survival curve for MM patients not in renal failure versus those in renal failure

to chemotherapeutic regimen is as shown in Table 3. The patients who did not receive chemotherapy died before commencement of either cytotoxic or haemodialysis. Renal function test of 6 (35.2%) patients were corrected with administration of cytotoxic drugs, allopurinol and hydration. The remaining patients had varying degrees of partial recovery. Of the 14 patients with renal failure, 5(35.7%) had haemodialysis. Three (3) of the 5 patients who had haemodialysis died within 3 months of diagnosis and treatment.

The average survival time for all patients irrespective of renal status was 56 months after diagnosis. The survival curve for patients with renal failure compared to normal is shown in Figure 2. Patients with renal failure were more likely to have shorter survival rates. The cumulative survival at 3 and 15 months for patients with normal renal status was, 86.4% and 62.9%, respectively while it was 73.3% and 57% respectively for patients with renal failure ($p > 0.05$).

DISCUSSION

Renal disease is one of the major complications of MM particularly in the advanced stage with prognostic significance. Different criteria have been used to define renal insufficiency in patients. The incidence of renal insufficiency in our patients is comparable to published data using serum creatinine of 1.3mg/dl as cut off, but slightly higher proportion of patients are observed to have renal failure⁵⁻⁷. Some studies with similar or

higher percentage of renal insufficiency attributed it to advanced disease^{6,8}. The different criteria used to define renal failure and presence of other co-morbidity may be responsible for the different figures obtained. The spectrum of renal lesion observed in MM is quite wide and varied ranging from acute to chronic and tubular to lesion in the nephron⁴. More than one type of renal disease may be present in a single patient with several factors working together to provoke this complication. Acute renal failure accounts for 50% of it, Often this may be precipitated by dehydration, hypercalcaemia, infection, non steroidal anti-inflammatory drugs and radiological contrast⁴.

The frequency of hypercalcaemia was similar to findings in some other studies^{8,9}. The presence of hypocalcaemia often associated with renal failure may be responsible for an almost similar average value for calcium level in both circumstances. Chronic renal disease should be considered in patients with hypocalcaemia with the possibility of the initial cause being unrelated to multiple myeloma. The biochemical abnormality of multiple myeloma might have worsened the renal status. Reversibility of renal failure obtained in 35.2% of renal failure patients in this study is lower than 50% documented for other studies^{8,9}. Correction of hypercalcaemia has been linked to reversibility in those studies. The severity of renal damage may be responsible for the lower number of patients with reversible renal failure in the current study.

There are studies that demonstrated that recovery of renal function was also associated with the severity of renal failure and degree of proteinuria^{6,8,10}. The higher white cell count in patients with renal failure may suggest the presence of infection. Dehydration occasioned by hot weather that is peculiar to the tropics might have contributed to the degree of renal failure in these patients.

The high tumour burden (stage III) observed in 93% of our patients with renal failure may suggest the presence of cast nephropathy. Cast nephropathy has been identified to be an important underlying factor in patients with high tumour burden¹¹. In some renal biopsy studies of patients with myeloma and renal disease, 40 - 63% had cast nephropathy, 19 - 26% had light-chain deposition disease, 7 - 30% had amyloidosis, and <1% had cryoglobulinemic renal disease^{12,13}. Though renal biopsy results were not available for our set of patients, the presence of Bence Jones protein and amyloid deposition could not be completely ruled out considering the insensitivity of the heat method of BJP detection used in diagnosis. The role of cast nephropathy has been reported particularly when the creatinine is >7mg/dl¹¹, however, it might be difficult to ascertain its degree of contribution in this study. These patients could benefit from plasmapheresis^{14,15}. The lower haematocrit observed in patients with renal failure has also been linked with cast nephropathy⁴.

There is no doubt that the precipitating factor for renal failure in the patients is multifactorial, however, the incidence of hyperuricaemia is higher in the patients with renal failure compared to those without renal failure (43% vs. 27%) but the mean uric acid level showed that there was no difference, but when both groups were compared with renal insufficiency group hyperuricemia was significantly evident in the insufficiency group. Although the reason for this is not clear, it may be due to the fact that subjects in the renal failure group often present acutely requiring hydration and sometimes emergency dialysis which obviously would have affected their serum uric acid levels since blood sample might have been collected during resuscitation. High tumour burden is an established cause of hyperuricaemia. It is well known that rehydration, correction of hyperuricaemia and hypercalcaemia or discontinuation of nephrotoxic drugs often improve renal function. The higher percentage of patients with renal dysfunction in the younger age group was unexpected and contrary to the observation in other studies. Advancing age with median age of 58 years in developed countries has been associated with renal dysfunction^{5,16}. The younger patients in this study had higher incidence of hyperuricaemia and therefore more severe disease.

Haemodialysis provide a survival benefit for patients with end stage renal failure with 25% becoming independent of dialysis^{17,18}. The average time for those patients who had haemodialysis could not be determined due to insufficient follow up information. The patients with renal failure had poorer survival than those with normal renal function. The average time for those who recover renal function on cytotoxic drug and supportive treatment was 4 weeks. Co-morbidity may be responsible for early demise (<3 months) in some MM patients with renal failure. Thus individualized treatment is a veritable option to improve outcome. Newer approaches to management include allogeneic bone marrow transplantation and kidney transplant⁸. This may be particularly more important in the younger age group having renal failure. However, this modality of management maybe considered farfetched in a financially constrained economy.

The patients' response to chemotherapy were not encouraging though melphalan and prednisolone at conventional dose was observed to be more effective in our patients than VAD, this was probably the reason for switching from VAD to M+P. This is contrary to previous documentation about VAD being more effective in patients with renal failure than the alkylating agents. Although a meta-analysis of 6633 patients found no difference between MP and various multiple combination chemotherapy regimen and survival^{19,20}. The poor outcome with early mortality seen in this and other reports^{9,18} could be improved upon with the use of plasmapheresis and bortezomib based regimen particularly in patients with poor response to routine supportive therapy²¹. There is a need to evolve treatment strategies that would produce better outcome.

CONCLUSION

This study confirms the findings in previous reports that, the factors contributing to renal failure in the myeloma patients are multifactorial. We suggest high index of suspicion among clinicians to aid early referral. Newer treatment strategies should be employed in those with renal failure.

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