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Management and Evolution of Multiple Myeloma with Renal Failure in Developing Countries: The Case of the Sylvanus Olympio University Hospital in Lome, Togo

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Abstract

Background: Renal failure (RF) is a frequent complication during multiple myeloma (MM) and sometimes reveals the disease. The median survival of MM patients with RF is shorter than that of patients with myeloma without renal involvement. Although patient survival has been prolonged with the new therapies, the median survival does not exceed five to seven years. Few data on this subject are available in sub-Saharan Africa. **Objectives**: To describe the therapeutic management and evolution of MM with RF in a developing country like Togo. **Method**: This was a retrospective descriptive and analytical study which took place over a period of ten years (2010-2019) and included the records of patients with MM according to the 2009 and/or 2014 IMWG criteria, hospitalized or followed up in the nephrology and rheumatology departments of the CHU-SO with a GFR < 60 ml/min/1.73m^2 related to their myeloma. **Results**: During the study period, 78 patients with MM had renal failure (55.7%). Therapeutically, hygienic and dietary measures were dictated in 84.6% of cases (68 patients). Rehydration was performed in 38 cases (48.7%); alkalinization of urine in 10 cases (12.8%); use of antibiotics in 36 cases (46.2%), NSAIDs in 51 cases (65.4%); use of biphosphonates in 36 cases (46.6%). Surgical immobilization by screw-plate osteosynthesis was performed in 02 patients. Nephrologically, 8 patients underwent ESRD. The dif-

ferent chemotherapy protocols used were Melphalan-Prednisone in 70% of cases, Melphalan-Cyclophosphamide-Prednisone in 26.7% of cases and Cyclophosphamide-Prednisone in 3.3%. The median overall survival was 8 months. The median survival was 13 months in patients who recovered from renal failure versus 2 months in those who did not recover from renal failure ($p = 0.0030$). Of the 78 patients in our series, 22 patients had died (28.2%). **Conclusion**: Despite renal failure, the Alexanian protocol and biphosphonates are still widely used in combination with symptomatic treatment with significant results.

Keywords

Renal Failure, Multiple Myeloma, Management, Evolution, Togo

1. Introduction

Renal failure (RF) in multiple myeloma (MM) is defined as a reversible or irreversible decrease in glomerular filtration rate (GFR) secondary to MM-related renal injury and manifested by a range of clinical and paraclinical manifestations [1]. It is a frequent complication during MM and sometimes reveals the disease [1] [2]. The occurrence of RF and especially its persistence have a strong impact on patient survival. The median survival of MM patients with RF is shorter than that of patients with myeloma without renal involvement [3]. It is therefore a major cause of morbidity and mortality in patients with MM. Despite real therapeutic progress in recent years, relapse of the disease remains unavoidable, and MM remains an incurable disease at present. Although patient survival has been prolonged with the new therapies, the median survival does not exceed five to seven years. The prognosis varies between patients: some die within a few months, while others have a survival of more than 10 years [4]. MM is variously appreciated in the nephrological setting and has been for several years. The parameters that allow the discovery of MM to predict the renal evolution and the prognosis are not yet elucidated. Few data on this subject are available in sub-Saharan Africa. In Togo, to our knowledge, no study has been done on the subject, hence this study whose objective was to describe the therapeutic management and evolution of MM with RF in a developing country like Togo.

2. Material and Method

Our study was conducted in the nephrology-hemodialysis and rheumatology departments of the Sylvanus Olympio University Hospital (CHU SO) in Lomé. It was a retrospective descriptive and analytical study that took place over a 10-year period from January 1, 2010, to December 31, 2019, and included the records of patients with multiple myeloma hospitalized or followed in the nephrology and rheumatology departments of the CHU-SO. We included in this study any patient aged 18 years and older, hospitalized or followed up in nephrology or rheu-

matology at the CHU SO, in whom the diagnosis of MM was made according to the 2009 and/or 2014 IMWG criteria [5], who presented with a GFR < 60 ml/min/1.73m^2 related to their myeloma. We did not include in the study, patients with a GFR ≥ 60 ml/min/1.73m^2, nor those with renal failure unrelated to myeloma. We excluded from the study, patients with incomplete or unexploitable records.

Data were collected using pre-printed forms from hospitalization and consultation records and registers. The data collection form was used for the analysis of the observations. To optimize the use of the records, we had to rephrase some of the data to standardize them. The parameters studied were clinical (history of the disease, general signs, renal signs, and co-morbidities); paraclinical (blood and urine biological tests, morphological, cytological, and anatomical-pathological tests); therapeutic (symptomatic measures, hemodialysis, background treatment and maintenance treatment); prognostic and evolutionary (Salmon and Durie classification, the international staging system, response to treatment, complications of the disease and occurrence of death). The data collected were entered into a database designed with EPI data in its version 3.1. Statistical analysis was performed with SPSS (Statistical Package for Science Social) version 20 and Microsoft Office Excel version 2016. It was a descriptive analysis of the population. The quantitative variables were presented as mean and standard deviation and the qualitative variables were presented as numbers and percentages. From an ethical point of view, we obtained the agreement of the bioethics committee. The confidentiality of the biomedical data collected was ensured by the anonymity of the survey forms.

3. Results

3.1. General Data

During the study period, 16,429 patients were followed or hospitalized in the rheumatology and nephrology-hemodialysis departments of the CHU SO and MM was diagnosed in 140 patients. The prevalence of MM was then 0.9%. During the same period, of the 140 patients with MM, 78 had developed renal failure, including 60 patients (76.9%) from the rheumatology department and 18 (23.1%) from the nephrology department. Renal failure in MM was 55.7%. This renal failure was inaugural in 20 cases (14.3%), concomitant with MM in 32 cases (22.9%) and secondary to MM in 26 cases (18.6%). Thus, 42.9% of patients had RF at the time of diagnosis of MM. The annual incidence of IR in MM was on average 7.8 new cases/year. The mean age of the patients was 58.9 ± 11.0 years with extremes of 33 and 85 years with 53.8% men (42 cases) versus 46.2% women (36 cases), *i.e.*, a sex ratio (M/F) of 1.17. In terms of prognosis, all patients had been classified according to Salmon and Durie and then according to the international staging system (ISS). According to Salmon and Durie, 6 patients (7.7%) were in stage I-A, 4 patients (5.1%) in stage II-A, 4 patients (5.1%) in stage II-B, 38 patients (48.8%) in stage III-A and 26 patients (33.3%) in stage

III-B. Only 18 patients (23.1%) could benefit from the ISS classification: 2 patients were classified as stage 1 (11.1%) and stages 2 and 3 were found in the same number of cases with 8 patients each (44.4%).

3.2. Therapeutic Aspects

From a medical point of view, hygienic and dietary measures were prescribed in 84.6% of cases (68 patients). These measures included water intake according to diuresis and hydration status, discontinuation of non-steroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors and other nephrotoxic drugs. Rehydration was performed in 38 cases (48.7%); alkalinization of urine in 10 cases (12.8%); use of analgesics in 70 cases (89.7%), antibiotics in 36 cases (46.2%), NSAIDs in 51 cases (65.4%); recourse to blood transfusion was found in 44 cases (56.4%), biphosphonates in 36 cases (46.6%), diuretics in 6 cases (7.7%). Antihypertensives were used in 16 cases (20.5%) and antidiabetics in 10 cases (12.8%). Orthopedic immobilization with a corset or a cast was used in 28 patients (35.9%). Surgical immobilization by screw-plate osteosynthesis was performed in two patients (2.6%). At the nephrological level, 8 patients (10.3%) had recourse to extra-renal purification, in particular intermittent hemodialysis. Four patients had received 5 sessions each, two patients 4 sessions and the last two 3 sessions. No patient was dialyzed with a high permeability membrane.

Chemotherapy was used as background treatment in 60 (76.9%) patients. No patient had received a human stem cell transplant. The different chemotherapy protocols used were:

- The Alexanian protocol, which combines melphalan and prednisone, was administered in 42 patients, *i.e.*, 70% of cases.
- The MCP protocol, which combines melphalan, cyclophosphamide and prednisone, was administered to 16 patients (26.7% of cases). In two patients, this protocol was abandoned in favor of the Alexanian protocol after the 8th cure.
- The remaining two patients (3.3%) received the CP protocol, which combines cyclophosphamide and prednisone.

The median number of courses was 6.5. Half of the cases (50%) had received more than 6 courses of treatment, including 36.7% who received all 12 courses. Regularity of treatment was effective in 38 patients (63.3% of cases). Dose adjustment (halving the normal dose) of the molecules according to renal function was observed in 8 cases (10%). Maintenance treatment was initiated in 20% (12 cases) and consisted of prednisone.

3.3. Progressive Aspects

After each course of treatment, the patients' creatinine levels were measured during follow-up. Mean creatinine levels during chemotherapy are shown in Table 1. Kaplan-Meier survival analysis yielded a median overall survival of 8 months (range, 0 and 60 months). This median survival was 13 months (mean: 15.4 months) in patients who had recovered from their renal failure (total and

Table 1. Changes in mean creatinine levels and GFR during treatment.

	Workforce	Average Creatinine (mg/l)	Average GFR (ml/min/1.73m^2)
1st cure	58	18.83 ± 16.28	68.48 ± 42.24
2nd cure	42	12.86 ± 11.71	86.99 ± 35.78
3rd cure	46	11.83 ± 5.98	82.71 ± 26.99
4th cure	40	13.29 ± 8.29	82.91 ± 43.90
5th cure	32	10.72 ± 4.38	88.20 ± 30.56
6th cure	30	10.59 ± 5.03	90.80 ± 33.52
7th cure	28	12.51 ± 10.43	97.35 ± 47.69
8th cure	24	11.25 ± 5.41	95.46 ± 54.28
9th cure	24	11.37 ± 4.91	81.00 ± 30.11
10th cure	22	12.77 ± 9.20	84.23 ± 34.76
11th cure	22	8.39 ± 1.14	101.91 ± 12.42
12th cure	22	9.79 ± 1.79	88.23 ± 23.20

GFR: Glomerular Filtration Rate.

partial remission) compared to a median survival of 2 months (mean: 8.4 months) in those who had not recovered from their renal failure (no response or worsening) with a statistically significant difference (p = 0.0030).

Of the 78 patients in our series, 22 patients died, for a case fatality rate of 28.2%. The mean survival was 60 months for patients with stage 1; 47 months for those with stage 2 and 6 months for those with stage 3 ISS. There was a significant difference (p value = 0.0060) when comparing the mean survival of patients according to the stages of the ISS classification. The regular follow-up of our patients allowed the detection of complications in 52 patients (66.7%). Infectious complications were the most frequent in 30 cases (38.5%) followed by an alteration of the general state in 30.8% (24 patients). Hypercalcemia and hematological complications were present in 26.9% each (21 patients). Pathologic fractures were present in 11.5% (9 patients).

After a median follow-up of 3 months, the renal evolution in the 78 patients, including those who received or did not receive chemotherapy, was marked by a total remission in 26.3% of patients, a partial remission in 28.9%, a worsening in 15.8% and a lack of renal response in 28.9% of patients. A total of 44.7% of patients had no improvement in renal function. Comparing the mean creatinine level at admission and at the last follow-up in consultation or in hospital, there was an improvement in the latter but no statistically significant difference (p = 0.4674). On the other hand, a comparison of the mean GFR at admission and at the last check-up showed a statistically significant difference (p value < 0.0001). A final blood calcium level check-up was performed in 68 patients. The mean

value was 99.0 ± 11.3 mg/l (extreme: 76 and 120 mg/l). Hypercalcemia was present in 28 patients (41.2%) with persistent hypercalcemia in 23.5%. In 20 patients (29.4%), correction of hypercalcemia was noted, and the blood calcium level was always normal in 20 patients (29.4%).

4. Discussion

4.1. Prognostic Aspects

The Salmon and Durie classification were the reference method for the evaluation of the prognosis. In our study, stage III was predominant at the time of diagnosis, as in those of Gorsane *et al.* [6] and Fasola *et al.* [7], with stage III in 83.4% and 93% of cases, respectively. This can be explained by the delay in consultation and diagnosis for most patients in the African context. β2-microglobulin and C-reactive protein (CRP) are independent prognostic factors related to tumor mass. There is a correlation between their levels and survival in MM which has allowed a classification into three groups. The survival rates in these three groups are 54, 27 and 6 months, respectively [8]. Currently, there is a consensus of the International Myeloma Working Group (IMWG) (2009) regarding the prognostic parameters to be analyzed at the time of diagnosis of MM. According to this consensus, the prognostic evaluation of MM should include β2-microglobulin and albumin level to define the international staging system (ISS) and cytogenetic analysis of plasma cells by fluorescent in situ hybridization (FISH) technique [8] [9]. However, the rate of completion of this examination is very low in our practice.

4.2. Therapeutic Aspects

Symptomatic treatment aims at correcting the factors favoring the occurrence of renal damage. In our study, 48.7% of patients had benefited from rehydration and 12.8% from urine alkalinization. Symptomatic measures must be systematic, as they limit the precipitation of light chains and their aggregation with the Tham-Horsfall protein [10]. The means of correction of hypercalcemia, notably bisphosphonates, were used in 46.6% of patients. However, contrary to some authors [11] [12], we note that the use of bisphosphonates was more frequent in our study. However, their use must be cautious in the case of RF. Indeed, their elimination is essentially by renal route. Their accumulation may lead to nephrotoxicity and may also induce adynamic osteopathy in patients with CKD [4].

In our study, hemodialysis was performed in 10.3% of patients. Our result remains lower than that reported by Mayara (40.3%) [13]. However, none of our patients benefited from peritoneal dialysis or plasma exchange, not practiced in Togo. This low rate of dialysis in our series would be related to the low socioeconomic level of our population and the absence of social security coverage. Correction of anemia was achieved by blood transfusion when the hemoglobin level was below 7 g/dl. None of our patients had benefited from erythropoietin given, in our context, the diminished purchasing capacity in our patients.

Multiple myeloma remains a serious disease, however its management has undergone recent therapeutic progress. In our study, 76.9% of the patients had received background treatment. Most of them (70%) had received the Alexanian protocol (MP) which has remained for a long time the reference treatment for myeloma in subjects over 65 years of age with 53% of responding patients. The MCP protocol was administered in 26.7% of cases and a combination of cyclophosphamide and prednisone in 3.3%. The findings of our study were quite comparable to data from studies performed in developing countries. The MP protocol was most often used in more than 50% of cases [6]. These observations result from the non-accessibility of these molecules, the low economic level of our populations and the fact that the narrowness of our technical platform does not lend itself to them. In developed countries, protocols based on Bortezomib and/or immunodulators (Thalidomide, Lenalinomide, Pamalidomide) were the first-line indication in MM with renal involvement [12] [14] [15] [16] [17]. However, the 2016 IMWG recommendations listed Bortezomib-based protocols as first-line chemotherapy in MM with renal involvement. This is a grade A recommendation. These recommendations are a result of the effectiveness of these new therapies in inducing a hematological but also renal response and their lower renal toxicity not requiring adaptation to renal function about Bortezomib, Thalidomide and Pamalidomide [5].

4.3. Evolutionary Aspects

In our study, complete remission of renal function was observed in 26.3% of cases and partial remission in 28.9%. This result is superior to the findings of Gorsane *et al.* [6] and Abdoulkarim Abdoulkarim Omar *et al.* [18] who found renal remission in 11.11% and 11.94% of cases, respectively.

However, our result is also significantly lower than several case series [11] [19]. The use of thalidomide, bortezomib and lenalidomide-based therapies could explain the better renal response observed in these case series. Indeed, in the series of Jung *et al.* [19], improvement of renal function was observed in 84.7% of patients treated with thalidomide, and 72% of patients treated with bortezomib. A complete renal response was identified in 39.8% of all patients with 43% of patients treated with thalidomide and 28% of patients treated with bortezomib.

Kaplan-Meier survival analysis yielded a median overall survival of 8.0 months. This median survival was 13 months in patients who recovered from renal failure (total and partial remission) and 2 months in those who did not recover from renal failure (no response or worsening) with a statistically significant difference ($p = 0.0030$). The median survival was significantly shorter than that found in the study by Jung *et al.* [19] and Shi *et al.* [20] where the median survival was 17 months, which would be related to the use of new molecules. On the other hand, it is noted that in our patients in whom IR had persisted, survival was lower. This observation has been made in several series, in that of Shi *et al.* in China [20] and Ecotière *et al.* in France [21]. Indeed, in Shi's series, the median survival

of patients with improved renal function was 46.0 months compared with 13.0 months for those with irreversible renal damage [20] and in Ecotière's series, the median survival was 42 months for patients with renal response compared with 11 months for patients without renal response. Indeed, during renal damage and MM, the survival of patients depends essentially on two elements: the response to treatment and the severity of the initial renal damage. Therefore, renal recovery should be a major goal of therapy in MM with RF since patients who recover from RF have a similar survival to patients with MM without RF [10]. The death rate was 28.2% in our series. This rate is lower than that observed by Fasola *et al.* [7] in Nigeria, which was 37.1%.

4.4. Limitations of the Study

Our study, as with most cross-sectional studies, was confronted with the lack of certain information in the patients' medical records. Most patients came from the rheumatology department, which is not a reference department for the management of renal failure. Indeed, MM is a cancerous pathology, and its management is multidisciplinary, involving the oncologist, the hematologist, the rheumatologist, the neurologist, and the nephrologist. These difficulties could be a source of bias and thus limit our results. However, our study remains interesting because to our knowledge, it is the first study in Togo to provide management and evolutionary data on MM with RF in Togo.

5. Conclusion

We conducted a retrospective descriptive and analytical study covering a period of ten years in the Nephrology and Rheumatology Departments of the CHU SO of Lomé, with the objective of describing the therapeutic and evolutionary aspects of MM with RF in our Togolese context. Despite renal insufficiency, the Alexanian protocol and biphosphonates are still widely used in combination with symptomatic treatment with significant results. It is important to actively search for renal insufficiency in myeloma patients. The management of MM should involve multidisciplinary collaboration. There is also an urgent need to improve the technical facilities of our health structures to allow for more advanced examinations, including renal biopsy. The most recent therapeutic agents that improve the prognosis must be made available to Togolese patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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