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Predictive factors of therapeutic response in multiple myeloma in the Cameroonian subject: A multicentric study in Yaoundé

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Abstract

Background: There is lack of data on clinical, epidemiological and therapeutic factors that influence optimal clinical response in patients treated for multiple myeloma in Cameroon. **Aims and Objectives:** To evaluate the response of Cameroonian subjects to the treatment of multiple myeloma and to investigate the factors affecting treatment outcomes. **Study Design:** The study was a retrospective cohort, descriptive and cross-sectional study. **Setting:** We recruited participants from three reference hospitals in the town of Yaounde, the capital of Cameroon (Yaounde Central Hospital, Yaounde General Hospital and the Yaounde University Teaching Center). **Materials and Methods:** Medical records of patients followed up in the hematology units of these hospitals were reviewed and only those with complete clinical, biological and radiological information were included in the study. Relevant data from the files were collected using designed forms. The forms were handed over to a statistician for statistical analysis. **Statistics:** Quantitative variables were described using measures of central tendency and qualitative variables were described using percentages and numbers. Univariate analysis with the goal of determining the relationship between sociodemographic, clinical, paraclinical factors and clinical response. For multivariate analysis, we employed the Cox model. Statistical significance was set at $p < 0.05$. **Results:** A total of 48 patients were recruited for our study, 75% of whom were men (sex ratio of 3:1). The mean age of the participants was 56.23 ± 8 years. Myeloma secreting IgG was found in 47.9% of patients and the mean bone marrow plasmocytosis at the time of diagnosis was 34.3%. Many participants (72.9%) were diagnosed at stage III of the disease. Treatment regimens in use amongst our participants were melphalan – prednisone (52.1%), vincristine – melphalan – cyclophosphamide – prednisone (18.8%), melphalan – prednisone – thalidomide (14.6%), vincristine – doxorubicin – dexamethasone (8.3%), cyclophosphamide – doxorubicin – vincristine – prednisone (6.3%). Overall therapeutic response rate was 45.8% and median survival without disease progression was 301 days. Melphalan – prednisone – thalidomide protocol had the best response (response rate of 71.4%). Factors associated with good clinical response were CRP less than 6 mg/l ($p = 0.01$) and greater than 6 treatment cycles ($p = 0.003$). Factors associated with shorter duration of survival without disease progression after treatment were CRP higher than 6 mg/l ($p = 0.028$), ESR higher than 50 mm/hour ($p = 0.048$), serum protein levels higher than 80 mg/l ($p = 0.0286$) and platelet count less than 150000/µl ($p = 0.034$). However, multivariate analysis revealed that only CRP less than 6mg/l was associated with duration of survival without disease progression ($p = 0.018$). **Conclusion:** Response to therapy for multiple myeloma in the Cameroonian subject is lower than that described in scientific literature. Conventional chemotherapy is the most employed in our context. The best therapeutic response was observed with the melphalan-prednisone-thalidomide regimen and CRP was the sole predictive factor of the type and duration of therapeutic response.

Keywords: predictive factors, therapeutic response, multiple myeloma, Cameroon.

INTRODUCTION

Multiple myeloma is a blood disorder belonging to the group of malignant monoclonal gammopathies which are neoplasms arising from plasma cell disorders [1]. Multiple myeloma is a condition characterized by the proliferation of a clone of plasmocytes leading to excessive production of abnormal immunoglobulins [2].

Multiple myeloma, also known as Kahler disease, represents 1% of cancers and approximately 10% of malignant hemopathies in developed countries [3, 4]. It represents 2% of malignancy-related deaths [5]. The disease evolves in three classical phases: monoclonal gammopathy of undetermined significance (MGUS), asymptomatic myeloma and symptomatic myeloma. Clinical presentation associates alteration of the general state of the patient, bone signs, anemia, renal failure and hypercalcemia [6].

The overall 5-year survival rate varies from 10 to 50%, depending on the stage of the disease and treatment response [7]. The main treatment goal is to increase the survival rate of patients and to improve on their quality of life [7]. Treatment often results in periods of remission of varying durations marked by residual disease but which in most cases are followed by relapse [2]. Early management

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protocols relied on alkylating chemotherapeutic agents and management of symptoms [3]. The median survival of patients was around 3 years [3]. However, therapeutic advancements have led to longer survival periods with the introduction of hematopoietic stem cell transplants and new classes of drugs into the treatment protocols [3]. These are essentially immunomodulators and proteasome inhibitors which lead to longer remissions and survival durations [4, 5]. Evaluation of treatment response is essential for patient follow-up. It permits detection of disease relapse and thus modification of treatment protocols.

Treatment response in multiple myeloma varies from one individual to another and takes into account various clinical and paraclinical factors. Studies done on Caucasian populations have determined that advanced patient age, disease stage, renal disease, the levels of certain serum proteins, genetic abnormalities and the type of first-line treatment protocol used, are elements of poor prognosis [8, 9]. The overall survival of patients is longer in patients with optimal therapeutic responses [10]. Despite recent therapeutic advancements, cases of refractory multiple myeloma continue to occur. The identification of factors that influence optimal clinical response in these patients is necessary, so they can be attacked.

In our context, there is lack of epidemiological, clinical and therapeutic data. We therefore decided to evaluate the response of Cameroonian subjects to the treatment of multiple myeloma and to investigate the factors affecting treatment outcomes.

MEANS AND METHODS

We carried out a retrospective cohort, descriptive and cross-sectional study from the 1st of February 2015 to the 30th of April 2015 in three reference hospitals in the town of Yaounde (Yaounde Central Hospital, Yaounde General Hospital and the Yaounde University Teaching Center). We proceeded by recruiting all patients of Cameroonian nationality irrespective of age or sex, who had been diagnosed with multiple myeloma according to the South West Oncology Group [34] criteria, who provided written consent to participate in the study. Excluded from our study were:

- All patients whose medical records were deemed incomplete (lack of clinical and paraclinical information in their records).
- All patients who were lost to follow-up during study.

In our study, we defined the following terms:

Complete response

- Reduction of serum monoclonal content by 90% or more from baseline values and/or:
- Plasmocytic infiltration of bone marrow less than 5% and/or:
- Total amelioration of clinical signs, absence of new bone lesions and return to baseline values of biological parameters (serum calcium, and protein electrophoresis) linked to the proliferation of plasmocytes (except irreversible signs).

Partial response

- Reduction of serum monoclonal content by 50% or more from baseline values and/or:
- Reduction of plasmocytic infiltration of bone marrow by at least 50% from initial values (if initial values were ≥ 30%) and/or:
- Moderate improvement of signs present at diagnosis.

Progressive disease

- Increase of serum monoclonal content by more than 25% from baseline values or increase in plasmocytic content of bone marrow and/or:
- Aggravation of clinical and paraclinical signs associated with plasmocytic proliferation.

Stable disease: Disease which does not correspond neither to criteria for complete response, partial response nor progressive disease.

Good response: Indicates complete or partial response.

Poor response: Indicates stable or progressive disease.

Survival without disease progression: Defined as the period from the date of treatment initiation up until either start of disease progression, relapse or death irrespective of the causes.

Overall survival: Defined as the period from date of diagnosis until date of most recent patient updates or patient death irrespective of the cause.

Relapsing disease: Defined as recommencement of clinical and paraclinical signs of disease associated with plasmocytic proliferation after a period of therapeutic response.

Hematological complications: Defined biologically as presence of a cytopenia or pancytopenia; or clinically as presence of anemia, bleeding or recurrent infectious syndrome.

Bone complications: Defined as presence of invalidating bone pain, pathological fractures, hypercalcemia or spinal cord compression.

Renal complications: increased serum creatinine to values over 20mg/l.

STATISTICAL ANALYSIS

Data were collected on designed forms. Statistical analysis consisted firstly of description of the characteristics of our study population. Quantitative variables were described using means, standard deviations, medians, minimums and maximums and qualitative variables were described using percentages and numbers. We then proceeded with univariate analysis with the goal of determining the relationship between sociodemographic, clinical, paraclinical factors and clinical response. This was done by employing the Chi-square test and the Fisher's exact test (when the total number was less than 5). Kaplan-Meier curves were used to estimate survival rates and results compared with the log-rank test. For multivariate analysis, we employed the Cox model; adjustments were done for age, sex, presence of comorbidities, disease stage and received treatment. Statistical significance was set at $p < 0.05$.

RESULTS

Sociodemographic, clinical and paraclinical profile of the study population

At the end of our study, 48 patients were recruited, with a sex ratio of 3:1 in favor of men. The mean age of the patients was 56.23 ± 8 years (range from 40 to 77 years). The age group from 50-60 years was the most represented (26 patients), making up 54.2% of the population.

Osteoarticular signs were present in all of the patients. Bone pain location in decreasing order was as follows: diffuse (44.7%), vertebral (36.2%), limbs (10.6%), pelvis (2.1%). Bone tumefactions were observed in the thorax affecting the clavicle, ribs and sternum. Pathological fractures were present in the vertebral column of 17 patients, in the long bones of 9 patients, in the ribs of 2 patients and the in pelvis of one patient. Two patients presented multiple fractures.

Table 1: Hematological profile of patients

	Number (n=48)	Percentage (%)
Hemoglobin		
Mean (range)	8,6±2,3 (4,3-14)	
Anemia	34	70,8
White blood cells		
Mean (range)	5,5±2,5 (1,5-16)	
Leucopenia	12	25
Leucocytosis	1	2,1
Neutrophils		
Mean (range)	2,8±1,9 (0,7-12,1)	
Neutropenia	10	20,8
Platelets		
Mean (range)	215±82 (8-153)	
Thrombocytopenia	10	20,8
ESR		
Mean (range)	88,7±39,2 (8-153)	
Increased	30	62,5

Table 2: Results of biochemical tests performed on the patients

	Number (n=48)	Percentage (%)
CRP : Mean (range)	16,4±15,7 (1-61)	56,25
Increased	27	43,75
Serum protein		
Mean (range)	92,7±25,7 (52-195)	
Increased	31	64,6
Serum albumin		
Mean (range)	36,2±,8 (64-162)	
Hypoalbuminemia	20	41,7
Serum calcium		
Mean (range)	103±18,9 (1,8-40,7)	
Hypercalcemia	14	31,3
Beta-2 microglobulin		
Mean (range)	6,85±8,5 (1,8-40,7)	
Increased	15	31,3
Bence-Jones proteinuria		
Mean (range)	6,85±8,5 (1,8-40,7)	
Positive	10	20,8
Negative	26	54,2
Serum protein electrophoresis		
Gamma peak	36	75
Beta peak	4	8,3

Three immunoglobulin isotypes were found in the study population. They were isotype IgG in 23 patients (47.9%), IgA in 1 patient (2.1%) and free light chains in 3 patients (6.3%) of which 39.6% were kappa chains and 10.4% were lambda chains. Serum creatinine was increased in 17 patients (35.4%). Twenty-two (22) patients in our series had bone marrow aspirates performed. Mean bone marrow plasmocytosis was 34.3±17.2%, with a range from 4 to 63% in the study population. It was at least 30% in 13 patients. Only 15 patients had had a bone marrow biopsy performed, which revealed plasmocytes in 12 of them. We found lacunar osteolytic lesions (54.2%), diffuse demineralization (52.08%), vertebral impaction (34.5%) and fracture lines (33.3%).

A majority of the patients presented with complications at diagnosis with the main one being bone complications which were present in 41 patients (85.4%).

Many of our patients were at Stage III of Durie and Salmon classification (72.9%). The International Staging System was applicable only to 19 patients (39.6%).

Treatment profile of the study population

Treatment was begun within 30 days following diagnosis in 70.8% of the patients. The chemotherapy protocols encountered were: MP (melphalan-prednisone), VMCP (vincristine-melphalan-cyclophosphamide-prednisone), MP-T (melphalan-prednisone-thalidomide), VAD (vincristine-adriblastin-dexamethasone) and CHOP (cyclophosphamide-adriblastin-oncovin-prednisone). The mean number of treatment cycles received was 5.8±4.12 (ranging from 1 to 24 cycles) with a median of 6 cycles. Pre-initiation therapy based on 5mg of dexamethasone tablets per day was seen in one patient.

Therapeutic response of patients

We observed complete response (CR) in 7 patients (14.6%) and partial response in 15 patients (31.3%) leading to a percentage of good response of 45.8%. The rate of poor response (PR) was 54.2%: stable disease in 16 patients (31.3%) and progressive disease in 10 patients (20.8%). The rate of CR was 28.6% for MP-T protocol, 25% for VAD protocol and 16% for MP protocol. Put together, polychemotherapy regimens (CHOP, VAD, VMCP) induced a good response rate of 37.5%. The mean duration of survival without disease progression was 301 days. As for overall survival, it was 573 days (ranging from 13 to 2923 days).

Determinants of therapeutic response

i) Factors predictive of the type of therapeutic response:

Patient age at the moment of diagnosis (before or after 65 years) did not significantly influence the response to therapy. There was no statistically significant difference between men and women.

Table 3: Relationship between CRP, ESR, beta-2 microglobulin and therapeutic response (univariate analysis).

	Poor response	Good response	OR (95% CI)	p-value
ESR				
≥	14	10	2,3	0,269
<	3	5	(0,4-12)	
CRP				
Increased	19	8	4,75	0,01
B2 micro globulin				
Increased	9	6	4,5	0,249

The presence of anemia, neutropenia or thrombocytopenia did not influence the type of therapeutic response in our sample. Increased CRP was predictive of poor therapeutic response. The link proved significant with p=0.01. No association was found between ESR and type of therapeutic response (p=0.269). Increased beta-2-microglobulin did not show any statistically significant relation with the type of clinical response either.

Neither immunoglobulin isotype nor the type of light chains had an impact on response to treatment. The percentage of plasmocytes on diagnosis was not linked to disease evolution under therapy.

There was no association between values of serum albumin, serum calcium, serum creatinine, serum urea, total serum protein, presence or absence of Bence Jones proteinuria and the type of therapeutic response.

The presence of complications (bone, hematological, renal, infectious) on diagnosis did not constitute a predictive factor of therapeutic response.

Disease stage, classified according to Salmon and Durie and the ISS classifications was not significantly associated with evolution of patients on chemotherapy.

None of the therapeutic protocols indicated statistically significant association with the type of response to therapy. On the other hand, number of chemotherapy cycles greater than 6 was a predictive factor of good response to therapy and also the type of response (p=0.03).

Table 4: Therapeutic determinants of response to treatment (univariate analysis)

	Poor response	Good response	OR (95% CI)	p-value
Biphosphonates				
Yes	12	12	0,71(0,22-2,23)	0,56
No	14	10		
Protocol				
MP	14	11	1,16 (0,3-3,6)	0,79
VMCP	6	3	1,9 (0,4-8,7)	0,324
MP-T	2	5	0,28 (0,04-1,6)	0,145
VAD	3	1	2,7 (0,2-28,4)	0,37
CHOP	1	2	0,4 (0,03-4,7)	0,436
Treatment cycles				
≤	17	5	6,4	0,003
>	9	17	(1,7-23)	

ii) Factors predictive of the duration of therapeutic response

Using univariate analysis, increased serum protein (p=0.0286), ESR ≥ 50mm/hour (p=0.048), increased CRP (p=0.028) and thrombocytopenia (p=0.034) were all biological elements associated with reduced duration of survival without disease progression. The duration of response was also influenced by the number of chemotherapy cycles received by the patient (p=0.05).

Table 5: Univariate analysis of the link between clinical and biological factors and duration of survival without disease progression (SWP)

Variables	SWP (median in days)	p-value	Variables	SWP (median in days)	p-value
Age			**Sex**		
≥ 65 years	244,5	0,68	Male	244	0,09
< 65 years	301		Female	474	
Anemia			**Neutropenia**		
Yes	266	0,17	Yes	474	0,125
No	495,5		No	275,5	
Thrombocytopenia			**ESR**		
Yes	181,5	0,034	≥ 50 mm	200,5	0,048
No	368		< 50 mm	802,5	
CRP			**B2 microglobulin**		
Increased	244	0,028	Increased	266	0,875
Immunoglobulin isotype			**Type of light chain**		
IgG	464	0,41	kappa	517	0,285
IgA	474	0,94	lambda	421	0,93
Plasmocytes			**Serum creatinine**		
≥ 30%	368	0,182	Increased	222	O,37
< 30%	15		Normal	474	
Blood urea			**Serum protein**		
Increased	244	0,054	Increased	266	0,0286
Serum albumin			**Serum calcium**		
Low	253,5	0,08	Increased	381	0,4
Bence Jones proteinuria			**Salmon and Durie**		
Positive	285	0,94	Stage 2	517	0,094
Negative	331		Stage 3	285	0,169

Table 6: Univariate analysis of effect of therapeutic and prognostic factors on duration of survival without disease progression (SWP)

Variables	SWP (median in days)	p-value	Variables	SWP (median in days)	p-value
Treatment regimen			**Number of treatment cycles**		
MP	266	0,548	≤ 6	15	
VMCP	293	0,472	> 6	480	
MP-T	361	0,824	**ISS stage**		
VAD	846	0,437	ISS 1	266	0,765
CHOP	1068,5	0,187	ISS 2	361	0,526
Biphosphonates			ISS 3	179	0,06
Yes	285	0,238			
No	390,5				

Multivariate analysis employing Cox's model revealed that only CRP values were predictive of duration of disease survival without progression.

Table 7: Multivariate analysis associated with therapeutic response.

Variables	Odds ratio	95% CI	p-value
ESR	0,15	0,0075-3,03	0,21
CRP	0,27	0,09-0,8	**0,018**
Thrombocytopenia	0,45	0,14-1,45	0,18
Serum protein	0,52	0,15-1,73	0,29

DISCUSSION

Sociodemographic, clinical and paraclinical profile of the participants

The mean age of the study population was 56.2±8 years. It was comparable to that found in 2014 by Doualla-Bija *et al* in a study carried out in the Douala General Hospital who obtained a mean age of 57±12.1 years [26] and also similar to that of Kakpovi Kodjo *et al* in a study in Lome who had a mean age of 56 years [16]. Our mean age was however lower than that found by Kyle *et al* in the USA who had a mean age of 66 years [15] and by Younes *et al* in Tunisia who had a mean age of 66.4 years [27]. Mean age of approximately 50 years was also found in other studies on Kahler's disease in sub-Saharan Africa [13, 14, 28]. This suggests that younger patient age is a particularity of multiple myeloma amongst black Africans.

Men were the majority in our sample with a sex ratio of 3:1. Ndomocrah *et al* in Bangui also found a sex ratio of 6.5 in favor of the male sex [33]. Fatou *et al* in their own series had a sex ratio of 1.44 in favor of men [13] and so did Koffi KG *et al* with a sex-ratio of 1.3 [16]. These findings did not corroborate with those of Doualla-Bija *et al* who had a female predominance of 63% [26]. A study carried out on a larger sample size by Kyle in 1975 revealed that multiple myeloma did not preferentially affect men or women [31].

Clinical presentation at the time of diagnosis was dominated by osteo-articular signs notably pain (97.7%). This was also found in literature from sub-Saharan Africa [13, 14, 26, 30] as well as literature from out of the African continent [15, 31]. The clinical signs found in these patients were varied (bone, hematological, neurological, nephrological). This confirms the necessity of multidisciplinary management of multiple myeloma.

As concerns paraclinical findings, IgG was found in 47.9% of cases. This was inferior to that found by Doualla-Bija *et al* (86%) and Koffi KG *et al* (72%) [14, 26]. Very few of our patients had multiple myeloma with IgA (2.1%) and none had myeloma with IgD or IgE, findings which were inferior to proportions found in literature. This could maybe be explained by the fact that only 56.3% of our study population had done this particular test. We, as did Fatou *et al*, found a predominance of kappa light chains over lambda light chains [13]. Mean bone marrow plasmocytosis in our study was 34.3%, similar to that found by Doualla-Biji *et al* who had 33% [26]. The most frequent radiological lesions found were osteolytic lesions. These lesions further consolidate the diagnosis of multiple myeloma in which malignant cells cause an exacerbation of osteoclastic activity and inhibition of osteoblastic activity [18]. Ndomocrah *et al* and Kakpovi *et al* found similar results [16, 30].

Approximately ¾ of patients were diagnosed at stage III of Salmon and Durie classification as against 25% and 2.1% for stages II and I. At diagnosis, most of the patients have advanced stage disease due to the non-specificity of symptoms, financial cost of laboratory investigations and late referrals. This results concord with that found in literature [14, 16, 26]. Sub-stage B of Salmon and Durie was found in 37.5% of our patients. The proportion of patients with kidney failure was higher than that in a study carried out by Blade J *et al* who had 22% [25]. This is explained by the late consultations and late diagnosis in the majority of patients. The prognostic ISS staging was applicable only in 39.6% of these patients. A few years ago, measurement of beta-2-microglobulin was not current practice in our context. Nevertheless, in patients who had this test done, a majority of them still had advanced disease.

Management

In our cohort, we found that 5 treatment regimens were employed. This was because of the multicentric nature of our study. Because of the lack of consensus on management of multiple myeloma in our national territory, treatment protocols vary from one center to another.

The Alexanian regimen was the most prescribed to our patients. This finding concords with that of other authors who use the Alexanian regimen as first-line therapy [13, 14]. This treatment option is normally prescribed to patients over the age of 65 years or to patients who present with severe comorbidities [4]. Meanwhile, the median age of the patients in our cohort was 55.5 years. The therapeutic options indicated for younger patients are often not easily prescribed in our context because of unavailability of these treatments by oral route which is necessary for their use. Moreover, the Alexanian regimen administered orally does not necessitate hospitalization, reducing the cost of management, permitting the patient to have a higher number of treatment cycles. A few of the patients received the MP-T regimen. This therapeutic regimen is the new reference treatment for patients over 65 years of age in developing countries [4] because thalidomide has anti-angiogenic effects which limits neovascularization which is indispensable for malignant proliferation. Its usage is not yet widespread in our context because of poor availability and high cost. The other treatment protocols found in our series were VMCP, VAD and CHOP. These polychemotherapy regimens are the most commonly

encountered in literature [13, 28, 30, 32]. None of the patients had received any treatment protocol based on proteasome inhibitors or bone marrow transplant or stem-cell transplant because of inadequate facilities in our context.

Therapeutic response in the population

The rate of good response was 45.8% in our study population with a rate of complete response of 14.6%. In our series, majority of patients had advanced disease. Late management could explain this poor response in our series. Non-compliance to treatment could also have played an important role: we noticed that there were sometimes lengthy durations between treatment cycles because of lack of finances. This reduced the treatment efficacy. The treatment response rate was lower than that found in literature which varied from one author to the other. Xu *et al* in China, in 2010, found a response rate of 69.2% in a population of 182 patients in a retrospective study [33]. Other authors have described results similar to theirs. Radon P *et al* in 2001 found a response rate of 62% in a study with 49 patients aged over 75 years and treated only with conventional chemotherapy [22]. Kyle RA *et al* described a good response rate of 67% in a study with 420 patients treated with polychemotherapy protocols and 14% complete response similar to the value we had [34]. Blade J *et al* described in 1994, 58% good response rate in a sample of 53 patients with multiple myeloma with IgD (76) and in 1996, 54% good response rate in a cohort of 72 patients with a minimum age of 40 years [36]. This disparity between response rates lies in the different treatment protocols and the different evaluation methods of therapeutic response which were not uniform in the different studies. Additionally, some authors were interested only in a particular age range of the population. The low rate of therapeutic response also suggests a racial hypothesis. Knowing that multiple myeloma affects the black race more [11, 12] and occurs at a younger age [13, 14, 16] compared to Caucasian populations, is it possible that black people have a higher frequency of high-risk cytogenetic anomalies (deletion of chromosome 13, 17p deletion, etc.) which lead to poor prognosis? The 45.8% rate of good response in our cohort reflects the response of patients treated with the Alexanian regimen (44%) because it was the most frequently prescribed (51.2% of patients). In literature, response to the MP regimen generally approaches a rate of 50% [3]; which concords with the results we obtained.

In our study, the MP-T regimen demarcated itself from other treatment protocols by its high rate of good response. This superiority of therapeutic response was also found in several randomized clinical trials comparing MP and MP-T protocols. The Italian group GIMEMA in a 2006 study including patients aged 60 to 85 years found a 76% good response rate in the group treated with MP-T and 47.6% in the group receiving only MP [20]. Results of the IFM 99-06 clinical trial also showed a statistically significant difference between the rate of good response in the MP-T and MP arms (76% and 35% respectively; $p<0.0001$) in patients aged 65 to 75 years (52). The IFM 01-01 trial found 62% good response for MP-T and 31% for MP ($p<0.001$) in patients aged over 75 years [21]. Waage *et al* in northern European population [37] and the HOVON 49 German study in patients under the age of 65 years [38], had similar results. New thalidomide-based treatment protocols therefore showed considerably better results in the management of multiple myeloma.

The rate of response to VAD in our series was less than that described in literature. We found a rate of 25%, inferior to that of MP. Alexanian R *et al* report a superiority of 15% of response to VAD as compared to response to MP [29]. An Algerian study also reported VAD overall response rate of 69% in its VAD arm [32]. This difference can be explained by the relatively small size of the VAD arm in our study (8.3% of our sample) compared to the groups in these other studies. A meta-analysis including 6633 patients from different clinical trials [19] showed a response rate higher in patients treated with polychemotherapy (60%) compared to the rate in patients treated with MP (53%). We however, found lower response rates in patients on polychemotherapy in our study population (37.5% for polychemotherapies versus 44% for MP). Seeing the small size of our sample, this difference is understandable.

The mean duration without disease progression was approximately 13 months with a median of about 10 months. Offidani *et al* had a mean duration of 23.5 months in a study including 66 patients [23]. This difference may have arisen because the treatment protocol used on all of his patients was the same and it was a protocol associating thalidomide while the majority of patients in our study were on the Alexanian protocol. Other studies revealed similar findings to that of Offidani *et al* [20, 21, 37, 38]. The duration of overall survival in our study was much inferior to that reported in other studies [10, 20, 21, 37, 38]. This is explained by the fact that our methodology did not include finding patients who were lost to follow-up. Additionally, the treatment response rate in our study was less than 50%. Early mortality could have been a consequence.

Factors predicting therapeutic response

No sociodemographic factor was found to be statistically significantly related to duration of survival without disease progression in our patients. However, many authors found that advanced age was a predictive factor of poor response and that it had a deleterious effect on survival without disease progression. This was the case of Xu *et al* [33] and Rodon *et al* [22]. We however noted that age did not affect survival in the study carried out by Waage *et al* [37]. Amongst our clinical findings, we found no predictive factor. The clinical factor most often found in literature was performance status [22]; however, this was not evaluated in our study because of lack of clinical data.

CRP was found to be a factor influencing both the quality of response to therapy and duration of survival without disease progression (multivariate analysis). This result can be explained by the fact that hepatic synthesis of CRP is stimulated by the production of interleukin-6. This cytokine is a recognized factor of growth and survival of malignant plasmocytes in multiple myeloma [17]. Studies by Safra *et al* showed that under-expression of the gene coding for interleukin-6 was a predictive factor of good response to treatment [39]. With levels of CRP being reflective of interleukin-6 levels, we deduce that high levels of CRP translate a higher level of interleukin-6 production. CRP therefore also is a predictive factor of the quality and duration of therapeutic response. This has been found by other authors [22, 23, 33].

Other paraclinical elements associated with duration of therapeutic response (univariate analysis) were ESR, serum protein levels and thrombocytopenia. In multiple myeloma, thrombocytopenia results from increased tumor mass (causing bone marrow failure) and therefore is secondary to advanced stage of disease. Increased serum protein levels and increase in ESR reflect elevation of monoclonal protein in plasma and consequently advanced disease stage. Thrombocytopenia also has a prognostic value on duration of survival without progression according to Rodon *et al* [22]. However, employing multivariate analysis, it lost its significance as a factor influencing survival without disease progression.

Beta-2-microglobulin has been identified by some authors as a predictive factor of the evolution of multiple myeloma [22, 33, 36]. Meanwhile, its impact on treatment was not shown in our work. This could be due to the fact that beta-2-microglobulin levels were not measured in the majority of our patients. Other elements affecting therapeutic response, like bone marrow plasmocytosis [33], serum creatinine [22, 36] were not found in our study. Our findings on serum creatinine were similar to those of Eleutherakis *et al* who found clinical response in patients with kidney failure to be similar to that in patients without kidney failure [24].

No particular isotype of immunoglobulins secreted by malignant plasmocytes was associated with response to treatment. This result was similar to that of Blade J *et al* who showed that therapeutic response to myelomas secreting IgD was similar to that of other myelomas [9].

Xu *et al* did not find any statistically significant difference between the different Salmon and Durie stages [33] and neither did we.

As concerns management, the use of bisphosphonates did not influence therapeutic response.

In our study, the use of a particular therapeutic regimen was not predictive of the type of therapeutic response. These results corroborated with those of the "myeloma trialists collaborative group) who did not find any statistically significant difference between survival without disease progression in patients treated with polychemotherapy regimens and that in patients on single-agent chemotherapy (p=0.6) [19]. Meanwhile, this meta-analysis showed a statistically significant difference between the rates of overall response (p<0.00001). Waage *et al* found non-significant difference when comparing survival without progress in patients receiving MP-T to those receiving MP+placebo [37] but a significant difference concerning the rate of good response in favor of MP-T (p<0.001). Other studies found a significantly longer duration of survival without progress and a better therapeutic response in patients on MP-T due to the heterogeneity of the different study populations. The number of treatment cycles was statistically significant for the type and duration of response. This was suggestive of that treatment efficacy is also dependent on the number of doses received.

CONCLUSION

At the end of our study, we demonstrate that response to treatment of multiple myeloma in the Cameroonian subject is lower than that described in scientific literature. With a wide variety of treatment protocols, conventional chemotherapy is the most employed in our context despite many patients being eligible for intensive treatment with peripheral stem-cell transplantation.

In the cohort we studied, the best therapeutic response was obtained with the melphalan-prednisone-thalidomide regimen. A link was established with serum protein levels after initiation of treatment. Multivariate analysis identified CRP as the sole predictive factor of the type and duration of therapeutic response.

Conflicts of interest

The authors did not receive support from any manufacturer or institution that may have led to bias or conflict of interest.

Authors' contribution

In our context, there is paucity of epidemiological, clinical and therapeutic data on multiple myeloma. The data provided by our study constitute a database which can be exploited locally and even regionally in our continent.

Our study also indicated the presence of infections which were a serious cause of mortality amongst our patients.

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