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Infection-Related Morbidity and Mortality among Multiple Myeloma Patients in West Africa

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Abstract

Context and objectives: Multiple Myeloma (MM) is characterized by immunosuppression leading to increased susceptibility to infections. The aim of this study was to evaluate the morbidity and mortality of infections in patients followed for MM.

Materials and methods: This was an 8-year retrospective, descriptive and analytical study (2015 to 2022) involving 108 patients. We included any patient followed up for MM diagnosed according to IMWG 2014 criteria and presenting with infection.

Results: Of 108 patients followed for MM, 60 patients had presented an infection (prevalence of 55.5%). Sex ratio (M/F) was 1.27 and mean age was 60.5 years (+/-12.09). Infections occurred more frequently in patients aged under 65 years, without comorbidities, with fewer than 2 CRAB signs and under 1st-line treatment protocol. Bacterial infections predominated (90%). CTD protocol was more associated with infections (50%). Fever was the most frequent sign (76.7%). Pulmonary focus predominated (78%).The germ most frequently identified was pneumococcus (77%). Twenty-six patients died (43%) and main cause of death being infections (38.5%). Risk factors for death were age under 65 years and 1st-line treatment ($p<0.05$). Death occurred within 1 year of the onset of infection in 50% of cases. Overall survival for patients without infection was 62%and 38% for patients with infection (p=0.00).

Conclusion: This study shows that infections in MM occur most frequently in patients under 65 years, with no comorbidities, fewer than two CRAB signs and in first-line chemotherapy. Infection is a major risk for mortality, as well as for morbidity, leading to higher costs of care, with prolonged hospitalization and costly long-term anti-infectious therapy.

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Introduction

Multiple Myeloma (MM) is a rare haematological malignancy that mainly affects the elderly. It accounts for around 10-15% of haematological cancers, making it second only to lymphomas in terms of frequency. MM is responsible for 15-20% of haematological cancer deaths, and around 2% of all cancer deaths [1].

Infections are a major cause of morbidity and mortality in MM patients, due to the immune deficiency inherent in the disease and its therapies. MM patients are at up to ten times greater risk of bacterial and viral infections than the normal population, mainly as a result of hypogammaglobulinemia and B-cell depletion secondary to MM pathogeny [2,3].

Over the last decade, the risk of infection has changed with the evolution of therapies, and other types of infection, notably fungal and viral, have been observed. Therapeutic advances and the growing number of treatment regimens mean that MM is a chronic pathology whose immunosuppression, and by extension the risk of infection, is increasing in tandem [2,3,4].

In Africa, most studies have focused on infections in haematological malignancies, but not specifically on MM. These studies have often focused on the frequency of occurrence of infections, and have not examined the general characteristics of these infections or the profile of patients presenting with these infections [5,6].

The nature of these infections is poorly understood in Africa, and anti-infectious treatment is still based on Western recommendations [7,8]. The aim of this study was to assess the morbidity and mortality associated with infections in patients undergoing treatment for MM.

Materials and Method

Patients: The study included all MM patients with documented infection followed at the clinical hematology department of the National Blood Transfusion Center in Dakar (Senegal).

Patients were diagnosed according to IMWG 2014 criteria [9] and received in consultation or hospitalization. Clinical, biological and radiological criteria were matched to arrive at a diagnosis of infection.

Infection was considered when at least one of the following criteria was present: thermal disturbances (fever ≥38°C, hypothermia ≤35°C); evidence of a clinical or imaging focus of infection; identification of germ in bacteriological, parasitological and/or mycological examinations.

Even in the absence of a documented germ, the presence of an infectious symptoms or an isolated fever was considered an infection.

Method

We conducted a retrospective, descriptive and analytical study spanning an 8-year period (2015 to 2022).

- General baseline characteristics of MM patients were:
- Epidemiological data: age, sex, professional activity, geographical origin, comorbidities (arterial hypertension, diabetes, hepatitis), lifestyle (smoking, herbal medicine, exposure to toxic substances).

Assessment of MM morbidity: evaluation of performans status (WHO PS), CRAB signs [9], prognostic stages (ISS) [9], other complications (spinal cord compression, pathological fracture).

Therapeutic aspects of MM: type of protocols (VCD, CTD, MPT, VRD), treatment phase (induction, maintenance), modalities (1st-line treatment, others lines treatment, relapse), therapeutic response (complete, partial, no response) [9].

- Infection-related morbidity: frequency of infection, type of infection, time of occurrence (at diagnosis, during treatment, at end of treatment, in relapse), risk factors for infection,
- Management of infections:
  - Diagnosis: blood count, inflammatory tests, germ isolation tests (blood culture, urine cytobacteriological test, viral serology test), biological secretions test, chest x-ray.
  - Treatment: broad-spectrum antibiotic therapy (directed according to the germ identified); other (antifungal, antiviral, antiparasitic); preventive treatment with antibioticby Cotrimoxazol associated Sulfadoxine and antivirals drugs.
- Mortality and characteristics of deceased patients: death rate, causes of death, risk factors for death, profile of deceased patients, overall survival.
- Statistical study: Data were entered into an Excel file and analyzed using SPSS (Statistical Package for Social Sciences) Statistics version 25. Results will be presented as means and standard deviations for quantitative parameters, and as percentages for qualitative parameters. The Shapiro test will be used to test for normality in the distribution of variables. Pearson correlation will be used to determine the strength of association. Also, using cross-tabulations between variables, we calculated the relative risks associated with death, as well as confidence intervals with a significance level ($p<0.05$). The study of survival was carried out on SPSS using the Kaplan Meier estimator.

Results

Of the 108 patients followed for MM, 60 patients had developed an infection, representing a prevalence of 55.5%. The sex ratio (M/F) was 1.27 and mean age was 60.5 years (+/-12.09).

The occurrence of infections was more frequent in patients aged under 65, without comorbidities, with fewer than 2 CRAB signs and under 1st-line treatment protocol (during the induction phase) **(Table I)**.

The majority of patients (78%) had presented a single infectious episode. Bacterial infections predominated (90%). Infection occurred most frequently during the induction phase of treatment (42%). The CTD protocol was more associated with infections (50%) **(Table II)**.

Fever was the most frequent infectious warning sign (76.7%). A pulmonary focus predominated, accounting for 78% of cases **(Table III)**. The germ most frequently isolated during infectious events was pneumococcus (77%) **(Table IV)**.

Twenty-six patients died (43%). The main cause of death was infection (38.5%) **(Figure 1)**. Mortality was predominantly in men (65.4%); pneumococcus was the predominant germ (42%); IgG kappa type of MM (73%) was more frequent in deceased patients; 42% of deceased patients were on CTD protocol. Risk factors for death were age under 65 years and 1st-line treatment **(Table V)**. Death occurred at 1 year from the onset of infection in

50% of cases. Overall survival for patients without infection was 62% and 38% for patients with infection (p=0.000) **(Figure 2)**.

Table 1: Factors influencing the occurrence of infections for myeloma patients.

Variables Number (n=60)	Frequency (%)	p. value
Gender		
Female	2236.7	0.773
Male	38	63.3
Age		
< 65 years39	65	0.012
≥ 65 years21	35	
Comorbidity		
No	42 70	0.049
Yes	18	30
CRAB signs		
<2	44	73.30.003
≥ 2	1626.7	
Period of infection		
Before myeloma treatment	22	36.70.027
During treatment	38	63.3
Myeloma Treatment Protocol		
1st line	44	73.20.037
Other lines	16	26

Table 2: Infectious events, types of infection, time of onset and treatment protocols.

Parameters Number (n=60)	Frequency (%)	
Number of infectious events		
1	47	78
2	09	15
3	03	5
4	01	2
Types of infection		
Bacterial	54	90
Parasitic	02	3
Viral	02	3
Fungal	02	3
Onset of infection		
Diagnostic	22	36
Induction phase	25	42
Maintenance phase	11	19
Relapse phase	02	3
Treatment protocols		
CTD	30	50
MPT	19	32
VTD	11	18

CTD: Cyclophosphamide-Thalidomide-Dexamethazone; MPT: Melphalan-Prednisone-Thalidomide; VTD: Velcade-Thalidomide-Dexamethazone.

Table 3: MM Patients' clinical presentation.

Clinical signs Number (n=60)	Frequency (%)	
Infectious warning signs		
Fever	46	76.7
Hypothermia	01	1.7
Night sweats	01	1.7
OMS PS>2	12	20
Focus Infectious		
Lung	46	78
Cutaneous/ bedsore	02	3
Digestive	01	1.7
Ocular	02	3
Malaria	02	3
Urinary	05	8

Table 4: Type and frequency of germs identified during infectious events.

Pathogens identified	Number (n=60)	Frequency (%)
Pneumococcus	46	77
Acinetobacter	1	2
Escherichia Coli	2	3
Staphylococcus	1	2
Klebsiella	1	2
Enterobacter	2	3
Candida Albicans	1	2
Plasmodium Falciparum	2	3
Streptococcus Aureus	1	2
SARS-CoV-2	2	3

Table 5: Risk factors associated with MM patient's death.

Variables	Patients deceased (n=26)	Living patients (n=34)p	
Gender			
Female	09	13	0.773
Male	17	21	
Age			
<65 years	16	27	0.012
≥ 65 years	10	07	
Comorbidities			
Yes	19	23	0.05
No	07	11	
Treatment protocols			
CTD	11	19	0.406
Others protocols	9	10	
Occurrence of infection			
Before treatment	10	12	0.038
During treatment	16	22	
Therapeutic line			
1st line	20	24	0.027
Other lines	06	10	

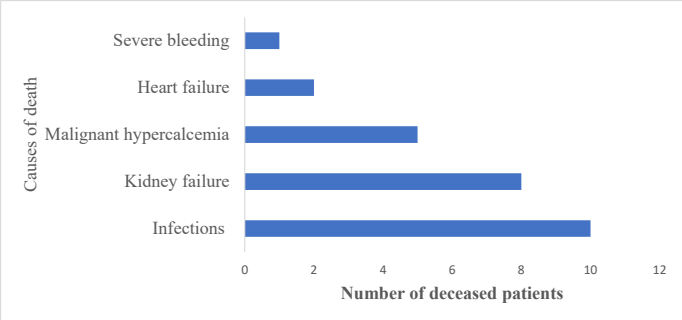

Figure 1: Distribution of patients by cause of death.

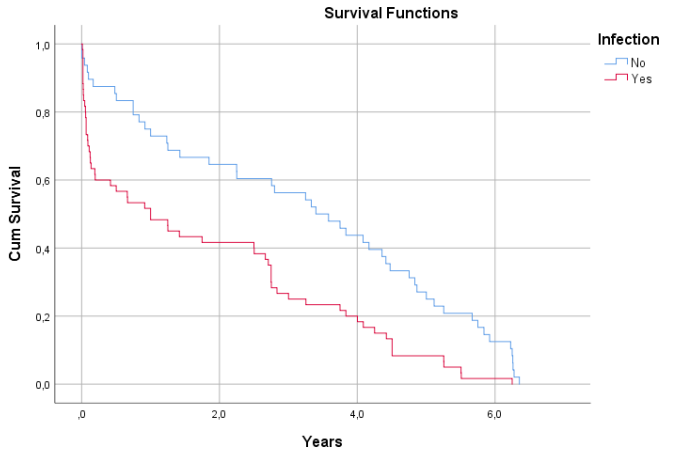

Figure 2: Comparison of patient's overall survival. (MM with infections versus MM without infections)

Discussion

Risk factors for the occurrence of infection:

According to the occurrence of infection, there were no statistically significant differences according to gender, to MM type, to prognostic stage (ISS) and therapeutic response. However, infection was more frequent in patients under 65 years with no comorbidity and fewer than two CRAB signs. Infection occurred in the majority of our patients during the induction phase of treatment (45%). This result differs from that of Brioli A [10], who found 34% of infections at diagnosis, and Fall S in Senegal [5], who found 23.5%. This difference is probably linked to the delay in diagnosis, but also to non-compliance with domestic and environmental hygiene measures. The CTD protocol was more associated with the occurrence of infection (50%). It has been reported that this protocol favors the occurrence of infections in MM, because in addition to the immunosuppression caused by MM, cyclophosphamide leads to cytopenias (severe neutropenia) and dexamethasone to immunosuppression [11]. This justifies systematic anti-infectious prophylaxis in patients treated with the CTD protocol.

Morbidity of infections in myeloma:

In studies of infectious complications in haematological malignancies, several authors have highlighted the predominance of invasive infections in MM. The frequency of infections in myeloma varies from several study. Brahem M [12] in Tunisia found a rate of 38.3%, Carvalho AS [13] in Australia (10.6%), Mert D [39] in Turkey (4.5%) and Cattaneo C [14] in Italy (11.8%). This could be explained by the fact that MM induces a humoral immunity deficiency linked to hypogammaglobulinemia, sometimes profound, which results in an increased risk of infection, mainly with encapsulated germs, or increased by chemotherapy when it induces neutropenic phases, or by corticosteroids, even in the absence of neutropenia.

Infection occurred at the time of diagnosis in around 23.5% of patients, remaining a classic finding [5]. Fever was the most frequent infectious warning sign in our series (76.7%). This has been reported in the literature by Durand P [15]. Any fever is a priori evidence of an infectious state during the course of MM. Its occurrence is very frequent and constitutes a diagnostic and therapeutic emergency, as the patient's vital prognosis is threatened.

The pulmonary focus is most frequently described in our patients, as reported in other studies [16]. Other authors have reported a higher frequency of pulmonary infections, sometimes involving more than 50% of patients [15,17]. Infectious diseases are mainly documented by frontal chest radiography (58.3% pathological findings in our series) and blood cultures (54.5% positive in our series). The initiation of anti-infectious treatment should not be delayed by the results of complementary examinations, as the negativity of infectious research does not contraindicate anti-infectious treatment, which is often guided by clinical data [18,19].

The majority of our patients (78%) had a single infectious episode. Similarly, Carvalho AS's study [13] showed decreasing rates of recurrence of infection, with 72.5%, 18% and 9.5% respectively. Prevention of these infections should be based on antibiotic prophylaxis and systematic vaccination against encapsulated germs (especially pneumococcus). Oral antibiotic prophylaxis is instituted in cases of profound hypogammaglobulinemia, and polyvalent immunoglobulin supplementation may be recommended in patients with hypogammaglobulinemia, after a first infectious episode.

Gram-positive bacteria, dominated by pneumococci (77%), were more frequently isolated by blood cultures. The predominance of staphylococcus (47.7%) has been described in other studies [20]. This may be explained by the fact that Streptococcus pneumoniae possesses numerous virulence factors, some of which confer resistance to opsonization and phagocytosis, and are found in the respiratory tract, whereas Staphylococci are saprophytes of the skin and mucous membranes [15,21].

Assessment of patient mortality:

After 8 years, the overall evolution of MM patients with infections showed an all-cause mortality rate of 43%. The main cause of death was infection (10/26 cases, or 38.5%). This has already been reported in the study by Brahem M [12,22], which found 37.5% of deaths related to infections.

Other causes of death included renal failure and malignant hypercalcemia. This has already been reported in the study by Fall S [5], who found 16.2% of deaths related to malignant hypercalcemia and 36.8% of deaths related to renal failure.

The profile of patients who died revealed that the majority were male (65.4%), aged under 65 years (70%) with comorbidities, with a pulmonary infectious focus (65%) due to pneumococcus (42%), under CTD treatment protocol. This is consistent with other studies showing a greater frequency of death in men and in subjects over 60 years of age, due to the frequency of comorbidities during this period of life [23,24,25].

The risk factors associated with death in these patients identified were age under 65 years, 1st-line treatment and CTD protocol. Comparing the overall survival of patients who died without infections and those who had infections, we found that the mortality rate was higher in patients with infections, with a statistically significant difference. Infection was associated with a significant reduction in patient survival, as demonstrated in several studies [5,22].

Conclusion

Infection in MM is a life-threatening diagnostic and therapeutic emergency, sometimes requiring intensive care unit management. It is a major risk factor for mortality, as well as for morbidity, leading to higher costs of care, with prolonged hospitalization and costly long-term probabilistic antibiotic therapy. This study shows that infections in MM occur most frequently in patients under 65 years of age, with no comorbidities, fewer than two CRAB signs and in first-line chemotherapy.

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