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RESEARCH ARTICLE

SURVIVAL OUTCOME OF MULTIPLE MYELOMA PATIENTS ON CHEMOTHERAPEUTIC REGIMENS IN THENIGER-DELTA NIGERIA

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ABSTRACT

Multiple myeloma (MM) is one of the commonest hematological malignancies of public health importance in sub-Saharan Africa. Though primarily a disease of the bone marrow, it often poses a diagnostic dilemma for the orthopedic surgeons because of the frequent bone manifestations. Consequently, misdiagnosis and late presentation are often common contributory factors to the poor prognosis and survival of victims in Nigeria. There is dearth of information on the survival outcome of myeloma patients on chemotherapy in Nigeria prompting the embark on this study. **Methodology**: This was a retrospective study of patients diagnosed and managed for myeloma, over a period of ten years (2003-2013) in three hospitals in eastern Nigeria. Variables examined in the study included subjects' medical history, investigations, and chemotherapy. **Result:** The median age of patients was 60.6 years with male/female ratio of 2.3/1. 61.5%, 30.8% and 7.7% presented in Durie Salmon (DS) stages 3, 2 and 1 respectively. The mean survival interval was 39.2 months (95% CI, 32.0-47.2 months). 84.5% and 8% were on Melphalan plus Prednisolone (MP) and Cyclophosphamide plus prednisolone (CP) combination chemotherapies respectively while 7.5% were on triple regimen. The longest survival interval of 70 months was recorded by MP plus Bortezomib (VMP) triple regimen. **Conclusion:** The prognosis in multiple myeloma patients on chemotherapy is poor in eastern Nigeria. However, favorable outcome is recorded with triple regimen containing Thalidomide and Bortezomib.

INTRODUCTION

Multiple myeloma (MM) otherwise known as Myelomatosis or Kahler's disease is a clonal plasma cell disorder characterized by the presence of a monoclonal protein in the serum or urine, osteolytic lesions, increased plasma cells in the bone marrow, anaemia, and hypercalcemia.[1]It accounts for 1% of all cancers, 10% of all hematological malignancies, 19% of all deaths resulting from hematological malignancies. It also accounts for 1-2% of all cancer-related mortality.[2,3]In Nigeria, it represents 8.2% of all hematological malignancies.[4]The disease burden and mortality rate are twice commoner in Black people.[5] The age prevalence is 60 years and above ,relatively rare below 40 years. Two-thirds of newly diagnosed MM patients are more than 65 years of age globally. It is estimated that about 44.9% of MM subjects survive for about 5 year's post-diagnosis.[6]

The etiology of Plasma cell myeloma is poorly understood but studies have shown that the 2 known precursors to MM, monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), first described by Kyle and Greipp,[7,8] have risk of progression to MM.[9,10,11]Other factors with high relative risk ratio include immunosuppressive conditions such as HIV, bone marrow/organ transplantation, environmental exposures (pesticides, herbicides, asbestos, laxatives, hair dyes, ionizing radiations), and viral infections (Kaposi Sarcoma Herpes virus, hepatitis C virus, Ebstein-Barr Virus, and mutated cytomegalovirus) just to mention a few.[12] The therapeutic approach in the management of MM is based on a constellation of measures which include: correct diagnosis[13] clinical staging, counseling, multidisciplinary approach, supportive and definitive (chemotherapy and/or stem cell transplantation) treatments. Supportive intervention is a palliative treatment

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given to abate clinical presentations and improve quality of life of MM patients. The focus is to correct the deficits due to end-organ damage in MM subjects. These include hypercalcemia, renal failure, anemia, bone lesions and recurrent infections[14,15,16]. The chemotherapeutic approach encompasses the old conventional chemotherapeutic regimens and the new targeted regimens. The old regimens are sub-divided into the first line drugs (i.e. Melphalan), and the second line drugs {(such as Vincristine, Adriamycin and Dexamethasone (VAD); Cyclophosphamide, Vincristine, Adriamycin and Methylprednisolone (C-VAMP); and Adriamycin, Carmustine (BCNU), Cyclophosphamide and Melphalan, (ABCM)}. Chemotherapy may achieve Partial Remission (PR) or Complete Remission (CR). By CR we mean, achievement of 75% reduction of serum paraprotein, 95% reduction of initial urine Bence Jones Protein (if any), less than 5% bone marrow plasma cells and absence of clinical features present at the time of diagnosis.[17] In addition to the chemotherapeutics regimen mentioned above there are also other newer regimen available for MM management, otherwise known as target therapeutic regimen.[18,19,20]

The most advanced definitive therapeutic intervention on MM in this millennium is the stem cell transplantation (autologous and allogeneic). Although most suitable in younger age group (transplant-eligible), stem cell transplantation is the current trend in the management of MM globally. Autologous stem cell transplantation (ASCT) is most preferable definitive stem cell transplantation in MM subjects because it improves response rate and survival in patients with myeloma.[17,21]Although it is not a curative strategy, the response rates exceed 75% to 90%, with a CR rates ranging from 20% to 40% while OS of more than 4 years has been recorded[22,23] On the other hand, allogeneic stem cell transplantation is less preferable due to transplant-related complications and shorter OS compared to HDT-ASCT.

In developing countries such as those found in the eastern Nigeria, the diagnosis of MM is usually made after complications have set-in due to lack of manpower and facilities to initiate early diagnosis and institute prompt interventions. This ultimately leads to unfavorable outcome in MM management especially when the novel therapeutic regimens are not readily available or affordable. This study aimed at giving insight to the outcome of chemotherapeutic interventions on MM patients seen in eastern Nigeria. Currently there is dearth of surveys on this topic in developing countries.

METHODOLOGY

This was a 10 years retrospective study of Multiple myeloma cases in the departments of Hematology of University of Port Harcourt Teaching Hospital (UPTH), Braithwaite Memorial Specialist Hospital (BMSH), Port Harcourt, Rivers state and Federal Medical Center FMC), Umuahia, Abia state respectively. These three hospitals are located in south-eastern Nigeria. The study duration covered January 2003 to January 2013. The study included all subjects managed in this hospitals within the period stated.

Variables examined in the study included subjects' medical history, investigations, and chemotherapy. The Eastern Cooperative Oncology Group (ECOG) scale for measuring Performance Status (from 0 to 4) was applied to the patients with age adjustment index.[24]

Diagnosis of MM was established according to standard definition when at least two of the following criteria are met;[3]

1. Paraprotein detectable in serum or urine together with a subnormal concentration of at least one monoclonal immunoglobin.
2. ≥10% malignant plasma cells in the bone marrow
3. osteolytic and/or osteoporotic bone lesions compactible with Multiple myeloma.

Staging was according to DS Clinical staging.[25].

Ethical clearance was obtained from the Ethical Committee of the hospitals before review of relevant medical data of the patients. Statistical data were entered and analyzed using SPSS statistical software version 20.

RESULTS

Clinical Characteristics Of The Patients

Twenty six (26) patients (18 males and 8 females, M:F ratio 2.3:1 $p<0.05$) out of a total of 286 hematological malignancies managed within the study period met the inclusion criteria as MM subjects. This implies that 9.1% of hematological cancer subjects seen during the study period in the three hospitals had MM. The median age at presentation was 60.6 years (age range 45-81 years) with 7.7% of the patients below 50 years.

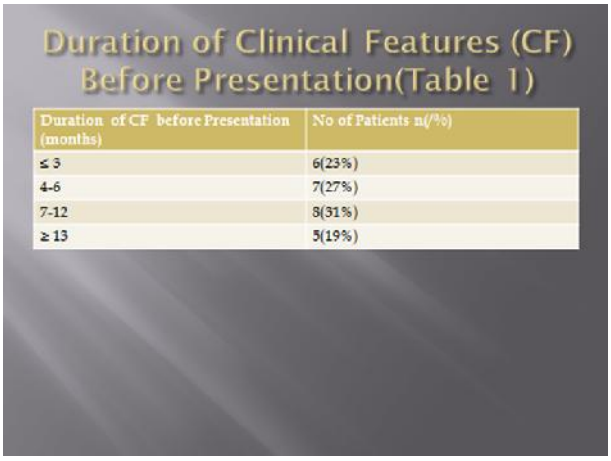
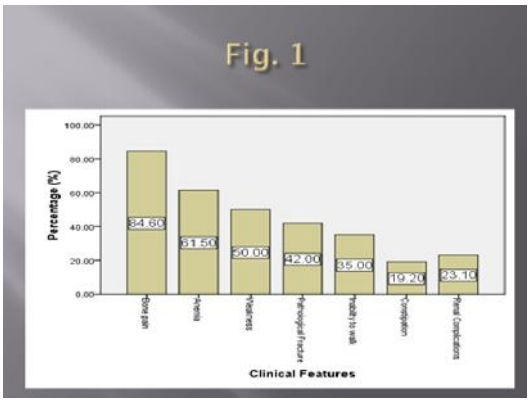
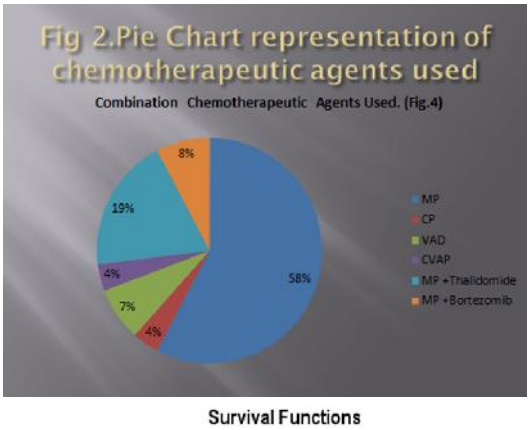


Table 2 P-values of Survival Outcome of MP and other Chemotherapeutic Regimens.Note:Data is not sufficient when the number of observation(s) is equal to one (n=1) for the test.

Var 1	Var 2	Duration V1	Duration V2	p-value
MP (n=15)	MPT (n=5)	42	48	**0.333**
MP (n=15)	VMP (n= 2)	42	70	**0.227**
MP (n=15)	CVAP(n=1)	42	2	**Null**
MP (n=15)	VAD (n=2)	42	8	**0.028**

There were 26.9% established history of environmental predispositions (exposure to agrochemicals, spray paint, rubber, hair dye, crude oil exploration, and petrochemicals). The median duration before presentation to the hospital was 11.89 months (1-48 months) (Table 1). 61.5%, 30.8%,and 7.7 presented in DS stages III,II and I diseases respectively. The mean survival interval was 39.6 months (95% CI,32.0-47.2). The clinical features at presentation are shown below with bone pains (84.6%) as the commonest presentation (Figure 1). ECOG Performance status of II-1V was recorded in 84.6% of the patients.





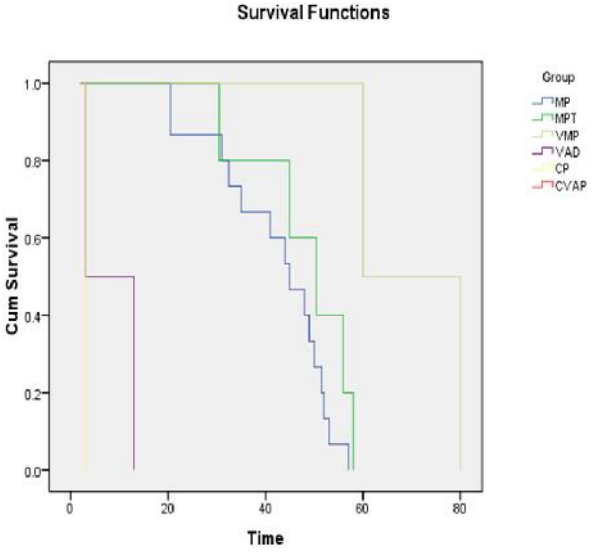


Figure 3 Median Survival Interval of chemotherapeutic agents used. VMP has the highest survival interval, while CVP has the least survival interval. (VMP>MPT>MP>VAD>CP>CVAP).

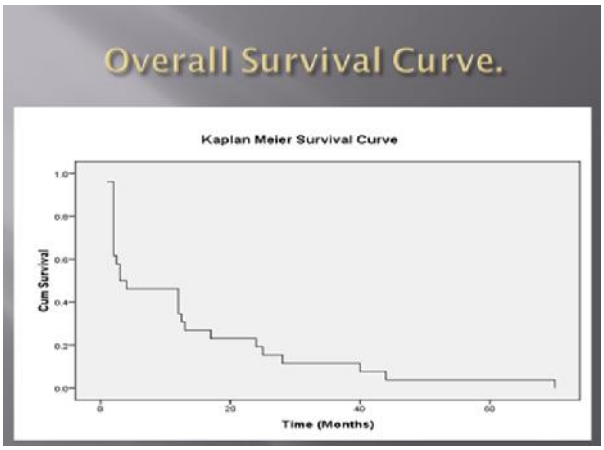


Figure 4 Kaplan-Meier curve showing the OS of MM patients seen during the study period.

Chemotherapeutic Agents

The Combination chemotherapeutic agents used by the patients were MP (58%), MPT (19%), and VMP (7.7%) VAD (7.7%), CVAP [Cyclophosphamide, Vincristine, Adriamycin and Prednisolone] (3.8%) and CP(3.8%). (Figure 2)

The p-values of the survival outcome of MP and other chemotherapeutic regimens is shown in table 2. The survival interval of MP (42 months) was shorter than that of MPT (48 months) and that of VMP (70 months) but this was not statistically significant. (P-value > 0.05 in each case). However the survival interval of MP is statically greater than that of VAD (8 months).

The median survival intervals of the various chemotherapeutic regimens used is depicted in figure 3 using Kaplan-Meier curves. The shortest median survival interval was recorded by CVAP (about 2 months), while the longest was by VMP (> 70 months).

The Kaplan-Meier curve of the overall survival of the patients is as shown in figure 4.

DISCUSSION

This study showed that MM has an incidence rate of 9.1% of all hematological malignancies seen during the study period. This was close to the 10% incidence rate in United States where MM accounts for the second most common hematological malignancy and constitutes 1% of all cancers[2,3,26]. Similar studies carried out in Nigeria reported incidence rates of 5.6% and 7.6% respectively[27,28]. These three hospitals are located in oil producing states in south-eastern Nigeria and this may account for the relatively higher incidence rate of MM based on the environmental pollution from oil spillage and flaring of gas by petrochemical industries in the region. The median age of 60.6 years observed in this study was similar to that previously reported in Western Nigeria,[27,29] but slightly differs from that by Omoti *et al* [28,30]which showed ages less than forties presenting with MM. This shows that multiple myeloma is a disease of the aged, although young-

aged MM patients are emerging in developing nations. The Male: Female ratio of 2.3/1 was in keeping with previous studies by Omoti, *et al*[28,30], but at variance with that of Salawu *et al*[27]. There are gender and racial disparities associated with MM and these tend to be more common in men and, for unknown reason, twice commoner in African-Americans compared to European-American.[5]

MP combination chemotherapy ranks the highest (84%) among chemotherapies used by MM patients in this region[27,29,30]. This may be as a result of their relative affordability, accessibility, tolerability and preferable clinical outcome in older transplant-ineligible patients that form the greater part of this study population. The very few patients who were on CP and CVAP (3.8% each) were unable to afford the standard anti-myeloma regimen and the OS interval recorded was short (table 2). The limited sample size of patients on CP and CVAP made it difficult to compare the outcomes of these regimens with MP. However, there was a significant difference between the outcome of patients who were on MP and those on VAD (P=0.028). This means that our patients did better on MP regimen compared with VAD triple regimen. Though limited by small sample size, this study revealed that younger transplant-eligible MM subjects responded favorably to immuno-modulatory and old conventional first line anti-myeloma combination chemotherapeutic regimens (MPT and VMP). Although there was no significant difference between the survival outcome of patients on MP with that of MPT (p=0.33) and VMP (p=0.227) triple combination chemotherapeutic regimens, VMP recorded the most favorable mean survival outcome of seventy months and the patient is still alive as at the time of this documentation. This is in keeping with previous study by Anderson *et al* which showed improved survival in MM with novel therapeutic agents.[31] This is highly commendable compared with an estimated overall survival period of 36-42 months from previous studies.[32,33] Most Bortezomib combination chemotherapies have better tolerability profiles and OS and they are currently used in maintenance therapy for MM patients who have attained CR .[34,35]

The survival interval of 39.2 months observed in our patients was higher than that observed previously by Omoti *et al*[30] and Madu *et al*[36], in the southern Nigeria but lower than that by Fasola *et al*[29] in Western Nigeria. This shows that much still needs to be done to improve the overall survival interval of myeloma patients in developing countries in terms of diagnosis and exploration of newer therapeutic interventions since these play significant role in improving the survival outcome of the patients. Although the survival rates vary in different geographical regions, remarkable advances in OS have been recorded. This paradigm shift in the survival rate of MM is tied to the impact of novel chemotherapeutic approach arising from better understanding of the molecular biology of the disease in developed countries.

CONCLUSION/RECOMMENDATIONS

Clinicians in developing countries need to exercise a high index of suspicion of multiple myeloma in any adult patient who presents with chronic bone pain in the health center after other possible causes have been excluded. While the older transplant-ineligible MM patients respond favorably to MP plus bortezomib or thalidomide-containing regimen, the young, good performance status but symptomatic MM patients tend to respond more favorably to immunomodulatory chemotherapeutic novel agents. However, the triple combination (eg VMP and/or MPT) regimens tend to have better survival outcome than MP-double-only combination chemotherapy in MM management in developing countries. There is therefore, need to improve the quality of life and survival expectations of MM patients in developing countries by taking advantage of major advances in chemotherapeutic and supportive options available.

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Disclosure Of Conflicts Of Interest

The authors declare that they have no relevant financial relationship(s) to disclose.

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