

Full Length Research Paper

Multiple myeloma: challenges of management in a developing country

¹Fasola FA, ²Eteng K and ³Akinyemi JO

Departments of Haematology ^{1,2}, Epidemiology and Biostatistics³
College of Medicine University of Ibadan, Nigeria, Department of Haematology, University College Hospital, Ibadan
Nigeria.

Abstract

The approach to the management of multiple myeloma has changed over the years with the benefit of longer life and fewer complications. There are considerable differences in the incidence and survival in different geographical areas. This study aims to assess facilities available for diagnosis and treatment to optimize the resources available for improvement in patient care. The medical records of all patients diagnosed with multiple myeloma within a ten year period in a referral hospital were reviewed retrospectively. All investigations and treatment strategies for the patients were assessed and subjected to statistical analysis. A total of 64 patients were diagnosed as multiple myeloma of which 72% had basic investigations required for diagnosis and treatment. The median age at presentation was 65years with age ranging from 36 to 85 years. Forty-three percent of the patients presented with prior symptoms of more than seven months duration. According to Durie and Salmon clinical staging 65% were stage 111. Anaemia, hypergammaglobulinaemia and hypoalbuminaemia were significant observations. Approximately 20% and 15% of the patients received radiotherapy and biphosphonate respectively. Seventeen percent of the patients were lost to follow up. The median survival time for the patients was 48 months after diagnosis. Causes of death include renal failure 6(30%), sepsis 6(30%), progressive disease 5(25%) and unrelated disorders 3(15%).Conclusion: The challenges in the management of these patients were late presentation with advanced disease and economic constraint. Taking this into consideration, patient survival and disease morbidity could be improved upon by fully incorporating recent advances in supportive care and adoption of health insurance and health planning in the management to reduce the economic burden of the disease on patients.

Keywords: Management challenges, myeloma, developing country.

INTRODUCTION

Multiple Myeloma (MM) is a malignant disorder of plasma cells proliferation. It is one of the commonest primary malignant tumours of the adult skeleton (Nau and Lewis, 2008). It accounts for 10% of all haematological malignancies in Caucasian (Kyle and Rajkumar, 2004 Rajkumar and Kyle, 2005,). Blacks have at least double the risk of being diagnosed with multiple myeloma and have twice the mortality rate from the disease compared to whites (Benjamin et al., 2003). Presentation is heterogeneous ranging from asymptomatic to severely

Symptomatic state with complications requiring emergency treatment. To distinguish multiple myeloma from other plasma cell dyscrasias, the diagnosis is based on histologic, serologic, and radiographic features. The criteria for the diagnosis of multiple myeloma are bone marrow with clonal plasma cells of at least 10% or histologic confirmation of a plasmacytoma and at least one of the following abnormalities; a monoclonal protein in the serum or urine (unless the patient has a nonsecretory myeloma [3% of patients]) and end-organ damage evidenced by renal insufficiency, hypercalcemia, anemia, or lytic bone lesions (International Myeloma Working Group, 2003, Rajkumar and Kyle, 2005). It is also important to recognize that the serum monoclonal

*Corresponding Author E-mail: folukefasola@yahoo.com

(M) protein can be small (oligo-secretory MM) or absent (non-secretory MM) in some patients with overt MM.

The diagnosis of multiple myeloma is often not that simple, it requires thoughtful synthesis of multiple variables from the patient's presentation. Approximately 20% of patients with multiple myeloma are recognized by chance without significant symptoms; such patients can be carefully monitored without instituting therapy (Dispenzieri and Kyle, 2005). In addition to clinical features and basic investigations such as complete blood count, skeletal x-ray, serum creatinine, urea and calcium levels, extensive investigations might be required to determine whether the damage is attributable to the myeloma or another cause. Once the diagnosis is made, most patients with active myeloma require systemic therapy. Before commencement of treatment, the disease is staged to guide therapeutic strategy. Durie–Salmon clinical staging system is the standard system based on a combination of factors that correlate with myeloma burden and renal function (Durie and Salmon, 1975). The prognosis may be determined using the International Prognostic Staging System (ISS) which though also reflects tumour burden and renal function, can predict survival irrespective of renal function and Durie and Salmon stage (Durie et al,1990).

The approach to the management of multiple myeloma has changed over the years. Therapy has evolved from control of symptoms and improvement of quality of life to ensuring durable remission with the benefit of longer life and fewer complications. These benefits are associated with emergence of costly treatment regimens which is not within the reach of most developing countries. There are suggestions by some authors of increasing multiple myeloma incidences over times which calls for a need to improve outcome of treatment in patients, regardless of location (Soutar et al, 1996). A critical look at the challenges of managing these patients might provide an opportunity to optimize the substantial advancement in the understanding of the biology and management of the disease. Perhaps there might be resources to harness for improvement of patient care and therapeutic outcome particularly in reducing mortality and complication of the disease. This study aims to assess facilities available for diagnosis and treatment and suggest ways to optimize the available resources for improvement of patient care.

MATERIALS AND METHODS

Medical records of all patients diagnosed with multiple myeloma between 2000 and 2009 were reviewed retrospectively. The study included all patients referred to and managed at the Haematology department of a tertiary hospital in Nigeria. The hospital is a 700 bed hospital with specialist in various aspects of medical and surgical practice. It serves approximately 5 million

Nigerians. Diagnosis of MM in the patients was according to the International Myeloma Working Group criteria (2003). Patients who did not fulfill the criteria were excluded from the study. Data reviewed included clinical features, duration of symptoms, and results of investigations. Treatments administered were documented with outcome. Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) (Oken et al, 1982).

The patients were referred to the hematology department by other physicians in same hospital and primary or secondary health center. All patients had bone marrow aspiration using posterior superior iliac spine. Other investigations requested for include full blood count, blood chemistry and serum protein electrophoresis. Immunoglobulin concentrations were measured by single radial immunodiffusion technique (mancini technique). The following immunoglobulins were measured IgA, IgG and IgM. The heat method was used to detect Bence Jones protein (BJP). Investigations and treatments were funded by patients and their relatives. . All data retrieved were summarized with descriptive statistics. The survival rate of patients was calculated from the time of diagnosis to death or lost follow up.

RESULTS

A total of 64 patients who had abnormal bone marrow plasmacytosis with either monoclonal protein and/or end organ damage were diagnosed as MM in the department during the study period. However, forty-six (72%) of the patients had sufficient basic investigations to determine the course or line of management of the disease. Forty patients had bone marrow plasmacytosis greater than 30% while 6 had bone marrow plasmacytosis between 10% and 30%. The median age at presentation for the patients was 65 years with age ranging from 36 to 85 years. Four percent of the patients were less than 40 years, while 24% were greater than 70 years. Male: Female ratio was 1.4:1. Forty (87%) attained secondary level of educational while 74% were retiree (pensioners).

Table 1, shows some of the symptoms at presentation. Other clinical features were jaundice, facial, pedal and abdominal swelling, reduction in urine output, passage of diarrhea stool, facial nerve palsy, altered level of consciousness, peppery sensation all over the body and stiffness of fingers. Co-morbidity was observed in 32.6% of the patients. The patients presented with multiplicity of symptoms. A performance status of ≥ 3 was observed in 83% of the patients. The patients who were referred to the haematologist by family physician, internist or orthopaedic surgeon had received some forms of treatment for their symptoms before referral.

The average duration of symptoms before the diagnosis and commencement of treatment are shown in Table 2. One of the patients had radiotherapy for

Table 1. Clinical features of multiple myeloma patients at presentation

Clinical features	Frequency	Percentage
Fatigue / dizzy spell	26	56.5
Bone pain	19	41.3
Back pain	23	50.0
Inability to work	18	39.1
Fever	16	34.8
Cough	14	30.4
Weakness of Limb	14	30.4
Co-morbid	15	32.6
Bony swelling	5	10.9
Pathological fracture	14	30.4
Bleeding	8	17.4
Weight loss	8	17.4
hepatomegaly	5	10.9
Splenomegaly	4	8.7

Table 2. Duration of symptoms before presentation to the haematologist

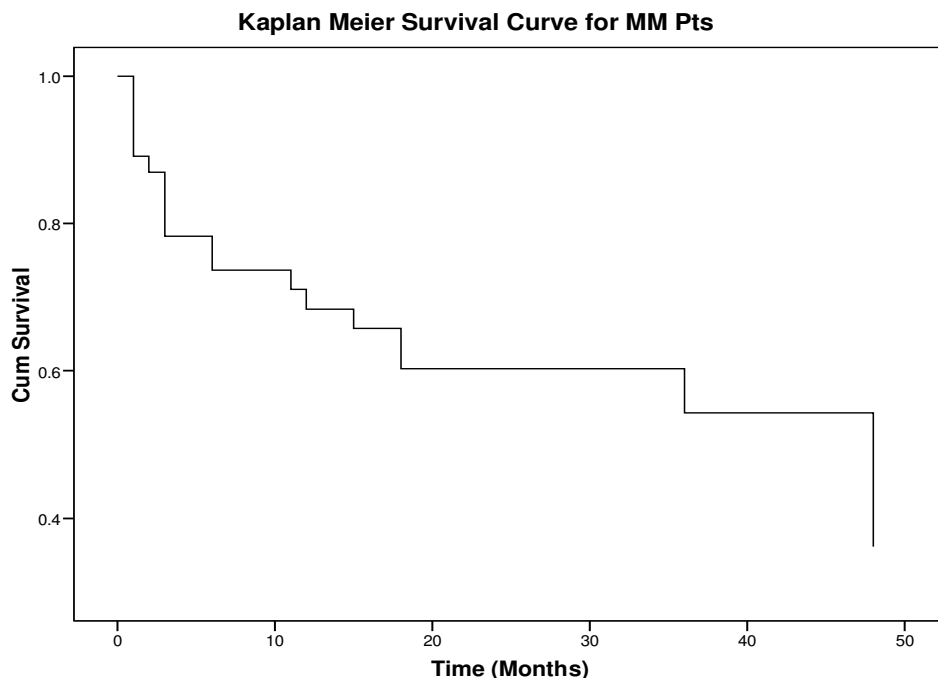
Duration in months	No of patients (%)
≤3	13 (28.3)
4-6	8 (17.4)
7-12	15 (32.6)
≥13	10 (21.7)

Table 3. comparison of the multiple myeloma patients' biochemical profile with reference range

Parameter	Normal Range	Patients :Mean (SD)	P-value
Total protein g/L	6.0 -8.0	9.2 (2.1)	< 0.05
Corrected calcium mg/dl	9.0 -11.0	10.3 (1.4)	>0.05
Uric acid mg/dl	2.0 -7.0	5.6 (4.6)	> 0.05
PCV %	36.0 – 52.0	24.0 (7.0)	< 0.05
WBC /mm ³	3000 – 9000	5167.9 (2241.7)	> 0.05
ESR mmhr ⁻¹	2 – 15	100.3 (37.3)	< 0.05
Platelet /mm ³	100 000 – 300 000	191786.2 (119420.1)	> 0.05
Globulin g/L	2.0 -4.5	6.1 (2.2)	< 0.05
Albumin g/L	3.5 – 5.0	3.1 (0.9)	< 0.05

plasmacytoma of the anterior chest wall and was diagnosed with MM 10 years later. Another patient had Open reduction and internal fixation previously on account of pathological fracture of the femur and was diagnosed with MM 3 years later. According to the Durie and Salmon clinical staging, 16 (35%) were stage II and 30 (65%) stage III disease. Results of laboratory investigations are summarized in Table 3. Patients paid for the basic investigations depending on availability of fund. Therefore, Immunoglobulin electrophoresis was available for 40(87%) patients, out of which 4(8.69) patients had biconal band and 26(72.2%) had thick monoclonal band while 10(27.7%) had normal protein separation. The remaining 6(16.6%) patients did not have result of serum protein electrophoresis due to lack of fund. Six (60.0%) of the 10 patients with normal serum

protein separation were positive for Bence Jones protein. The remaining 4 patients were diagnosed as non-secretory myeloma. Thirty - one patients had their serum immunoglobulin measured. The result from the quantitation showed elevated IgG; 15(48%) IgA; 6(19.4%) IgM ;1(3.2%), both IgG and IgA 2(6.5%). Serum immunoglobulin within normal range and immunoglobulin lower than normal range was observed in 4(12.9%) and 2(6.5%) respectively despite the presence of monoclonal protein on electrophoresis. Bence Jones protein was tested in 40 (87%) patients of which 15(37.5%) were positive. All patients had haematocrit, erythrocyte sedimentation rate, bone marrow aspiration and skeletal x-ray. Serum Uric acid, calcium, urea, creatinine levels were available for 37,36,43, and 40 patients respectively. Forty-six patients had total serum protein, globulin and



albumin level estimated. A comparison of the laboratory feature in the myeloma patients showed that the elevated erythrocyte sedimentation rate, low packed cell volume, elevated total serum protein and globulinaemia were statistically significant (Table 3).

The chemotherapeutic combinations available to patients were either melphalan and prednisolone (M+P) or vincristine, adriamycin and dexamethasone (VAD) based on their renal status. M+P regimen was administered to 20 patients. Vincristine, Adriamycin and Dexamethasone (VAD) at the recommend dose was given to by 5 patients. Twelve patients were observed to have poor response to VAD and were therefore, changed over to melphalan and prednisolone after one or two cycles. As at the time of analysis, 64% of those patients who received M+P were alive, with 40% and 60% of those who received VAD and VAD/M+P combination respectively. Nine (19.6%) patients did not receive treatment either due to early demise from complications or was granted request to be discharged from the hospital against medical advice, while 8 (17.3%) were lost to follow up after initial good response to treatment. Other available treatments include radiotherapy and biphosphonate which were received by 9 (19.6%) and 7 (15.2%) patients respectively. Five patients had haemodialysis. The median survival time for the patients was 48 months after diagnosis. Figure 1 shows the kaplan meier survival curve for the patients. Causes of death include renal failure 6 (30%), sepsis 6 (30%), progressive disease 5 (25%) and unrelated disorders 3 (15%). Five of the patients died during resuscitation with supportive therapy before commencement of cytotoxic therapy.

DISCUSSION

The occurrence of multiple myeloma is worldwide but there are considerable differences in the incidence and survival in different geographical areas. The difference in survival is often tied to therapeutic approach. The approach is guided by the protocol for diagnosis and available resources for management. Generally, myeloma remains incurable despite remarkable advances in understanding and management of the disease; however survival rate has improved over time. The challenges faced in the developed country may be a little different from that of the developing country. The survival duration in the developing countries could be as low as 7 months (Omoti and Omuemu, 2007) despite the use of melphalan and prednisolone which has been the standard treatment for over three decades.

The median age at presentation of patients as previously reported in the region (Salawu and Durosimi, 2005) is similar to that of the developed countries. In all the patients, myeloma led to progressive morbidity and eventual mortality by causing bone pain and skeletal destruction, hypercalcemia, anaemia, reduced resistance to infection and renal failure. In a minority of patients, bleeding diathesis was observed. The degree of bone marrow plasmacytosis and presence of complications in all the cases made the diagnosis straightforward. Basically, patients were seen at the hospital because of the complications of the myeloma. The investigations and management were carried out according to available fund although some were not done due to the non-availability of facility for such. One of the challenges faced by the managing physician, in such situation, particularly if the

diagnosis is not straightforward will be to distinguish between monoclonal gammopathy of undetermined significance, smouldering myeloma and myeloma (Kyle, 2001). The physician would also be tasked with identifying the role of myeloma when mild anemia or renal insufficiency and osteoporosis with compression fracture are observed in aged patients who may also have non-neoplastic etiologies or patients with comorbidity. Within the limit of available investigations, the patients could only be staged using the Durie–Salmon staging system. It is important to know that approximately 65% of patients staged as Durie–Salmon stage III could be International Prognostic Staging system (ISS) 1 or 2. Therefore there might have been constraints to providing more individualized information about the disease outcome which is required by patients and their families.

The patients presented to the haematologist with advanced disease and complications. This could to some extent be as a result of ignorance and apathy in seeking early medical attention due to its financial implication. Some of the patients had been on self medication before seeking medical attention. Lack of facility for early diagnosis may contribute to late detection of disease and referral to the haematologist. In addition, low level of suspicion by the healthcare provider in the primary and secondary health care facilities before reaching the advanced stage particularly in those who had symptoms for more than six months should be considered. Early diagnosis would have given patients the benefit of commencing definitive therapy before the advent of complication thereby reducing the economic burden of the disease. The classic CRAB measurement of calcium, renal function, anaemia, and skeletal survey (bone lesion) which are within reach of most health facilities referring the patients should be taken advantage of and included in the diagnostic protocol of patients suspected to have myeloma. Continue Medical Education to address early referral in this group of patients should be considered.

The frequency of clinical features and laboratory abnormalities were as documented in more technologically advanced setting (Kyle et al., 2003). However, this does not leave a doubt to the need for improvement in detection rate of the laboratory abnormalities. This study revealed that approximately 72% of the patients had the minimal required laboratory investigations. Despite the need for all patients suspected of having myeloma to do a serum and urine protein electrophoresis and immunofixation to determine the quantity and nature of the M protein (Rajkumar and Kyle, 2005), twenty-one percent of the patients could not have serum protein electrophoresis. This was attributed to lack of fund from the patient even though the facility was available. The incorporation of health insurance schemes and health care planning may help patients benefit optimally from the available resources. The diagnosis and management may be flawed in those patients whose M

proteins, a hallmark of the disease are not assessed. In the absence of the facility for immunofixation and quantitation for immunoglobulin D and E, certain group of patients might be left undiagnosed because small band or no evident M spike on serum protein electrophoresis is seen in IgD myeloma (Rajkumar and Kyle, 2005).

The detection rate of 37.5% in all patients for light chain in urine was low, therefore there is a likelihood of the proportion of patients with light chain in urine to be more than was actually reported. This is not surprising as the limitation of heat method is well established. The limitation is actually not reflected in the observation of 16% of our patients having light chain myeloma when it is taken into account that incidence elsewhere is 16 - 20% (Dispenzieri and Kyle, 2005; Rajkumar and Kyle, 2005). Could it be due to the abundance of light chains in the urine of patients with light chain myeloma only? To reduce the likelihood of underestimating the proportion of patients with light chains in urine, the use of urine immunoelectrophoresis or immunofixation for suspected cases of MM is imperative to increase the detection rate (Rajkumar and Kyle, 2005). The probability of overestimating the number of patients within the non-secretory myeloma category was high. Approximately two thirds of patients, previously designated as non secretory myeloma have a detectable immunoglobulin free light chain with the immunoglobulin free light chain (FLC) assay (Drayson et al., 2001). This was compounded with the possibility that patients presenting with complication of light chain deposition due to oligosecretion may be misdiagnosed. The FLC assay measures the level of free (unbound) κ and λ light chains in those with low serum and urine M protein levels serum. It is helpful for diagnosis and monitoring response in these groups of patients (Katzmann et al., 2002).

In order to substantially gain from the recent advances and reduce complexity in stratifying patients, the contribution of biological parameters as independent adverse prognostic factors should not be far-fetched to be annexed for patients' management. A review of tests available to myeloma patients in the region include basic tests of bone marrow aspiration, serum protein electrophoresis, immunoglobulin quantitation, renal function, complete blood count, calcium level and radiology (Omoti and Halim, 2007, Salawu and Durosimi, 2005). To further improve the management of patients, there is no gainsaying that the inclusion of β_2 microglobulin which is mandatory to stage patients using ISS should be included in the investigations. The test could be available in selected referral centers. The uncorrected β_2 microglobulin level increases as a result of both tumor burden growth and renal function deterioration. Being, a very sensitive indicator of glomerular filtration, it abrogates the independent prognostic value of the serum creatinine, urea and age in multivariate analysis (San Miguel and Garc'a-Sanz, 2005). A good marker of disease activity is Interleukin-6

(IL-6), a major plasma cell growth factor. An elevated serum levels have been associated with short survival.(Bataille et al,1989,Papadaki et al., 1997).This is an expensive test and may be unaffordable for resource limited countries. In search of an affordable test, serum C - reactive protein (CRP) levels represent a surrogate marker for IL-6 concentration (Bataille et al., 1992). The assessment of this protein is very simple and cheap, therefore CRP can replace IL-6.

Taking into account that patients often present with advanced disease and poor performance status (Omoti and Halim,2007), advances in supportive care were probably underutilized considering the use of biphosphonate in 15% of the patient despite the presence of bone changes in almost all the patients. Anemia was the most common hematologic complication. This was managed with red cell concentrate from the blood bank which is usually inadequately stock (Fasola et al., 2009). Recombinant human erythropoietin (rHuEPO) has been used to increase the hemoglobin level and improvement the quality of life of myeloma patients (Blade and Rosinol,2005). rHuEPO is easily available therefore its use in patients with anaemia is expected to reduce the use of blood transfusion from an already insufficient source.

The survival pattern of patients in literature ranges from a few months to more than 10 years (San Miguel and Garc'a- Sanz, 2005) .The median survival of 48 months observed in our patient is encouraging in spite of the challenges faced in diagnosis and treatment. Other studies in same region have reported poorer survival. The challenge posed by those patients who were unable to begin and sustain treatment may be managed with intense counseling. Social worker could also be involved in follow up of patients. The outcome of treatment with melphalan and prednisolone is comparable to that of more developed countries despite the challenges (Hussein, 1994, Blade et al., 1996). The appropriateness of melphalan and prednisolone for more than one third of the patients who are advanced in age with co-morbidity and poor performance status might have contributed to this result bearing in mind that myeloma remains incurable with current treatment approach. Therapeutic option plays a significant role in improving patient survival and reducing the emotional burden of the disease on patients and relatives. Further efforts are needed to expand opportunity for survival particularly of younger patients. New therapeutic options have led to substantial increase in survival expectations of younger patients with multiple myeloma in recent years. Cheaper alternative to the more expensive novel therapies such as thalidomide could be licensed for use. Treatment protocol would then include thalidomide with or without dexamethasone.

In conclusion, the survival of patients was as expected for the available treatment options though not without challenges. There is room for improvement in patients' management and outcome particularly in those patients who could not receive standard care due to economic

constraint. Even though it might be difficult to fix the economic problem, the adoption of health insurance and health planning might to a large extent increase access to standard care. Measures to encourage early referral can reduce complication. This can be through continuing medical education and adopting a protocol for diagnosis as well as cheaper alternative tests. More effort should be made to take advantage of the major advances in supportive strategies to reduce disease morbidity.

REFERENCES

- Bataille R, Boccadoro M, Klein B, Durie B, Pileri A (1992). C-reactive protein and beta-2 microglobulin produce a simple and powerful myeloma staging system. *Blood* 1992; 80: 733 – 737
- Bataille R, Jourdan M, Zhang XG, Klein B (1989). Serum levels of interleukin 6, a potent myeloma cell growth factor, as a reflect of disease severity in plasma cell dyscrasias. *J. Clin. Invest.* 84: 2008 – 2011
- Blade J, San Miguel JF, Fontanilas M (1996), survival of multiple myeloma patients who are potential candidates for early high- dose therapy intensification/auto-transplantation and who were conventionally treated. *J. Clin. Oncol.* 14:2167-2173
- Blade J, Rosinol LR(2005). hematologic and infectious complications in multiple myeloma. *Best Practice & Research Clinical Haematology* ;8 (4) :635 - 652.
- Benjamin M, Reddy S, Brawley OW (2003). Myeloma and race: a review of the literature. *Cancer Metastasis Rev.* 22(1) 87-93
- Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR (2001). Serum free light-chain measurement for identifying and monitoring patients with nonsecretory multiple myeloma. *Blood* 97(9): 2900-2902.
- Dispenzieri A, Kyle RA (2005). Multiple myeloma: clinical features and indications for therapy. *Best Pract. Res. Clin. Haematol.*18(4): 553–568.
- Durie BGM, Stock-Novack D, Salmon SE, Finley P, Beckord J, Crowley J, Coltman CA (1990). Prognostic value of pre-treatment serum B2 microglobulin in myeloma :A Southwest oncology Group study. *Blood*; 75:823 – 830.
- Durie BGM, Salmon SE (1975). A clinical staging system for multiple myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*;36(3):842-854.
- Fasola FA, Kotila TR, Shokumbi WA (2009). Audit of the red cell units supply of a busy hospital blood bank in Nigeria. *Niger. J. Clin. Pract.* 12(2):165-168.
- Hussein M (1994). Multiple Myeloma: an overview of diagnosis and management *Cleve Clin J Med*; 61(4): 285 -298
- International Myeloma Working Group (2003). : Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report of the International Myeloma Working Group. *Br. J. Haematol*; 121: 749–757
- Katzmann JA, Clark RJ, Abraham RS, Bryant S, Lymp JF, Bradwell AR, Kyle RA (2002). Serum reference intervals and diagnostic ranges for free kappa and free lambda immunoglobulin light chains; relative sensitivity for detection of monoclonal light chains. *Clin. Chem*; 48: 1437 – 1444
- Kyle RA (2001). Diagnostic challenges and standard therapy *Semin. Hematol.* 38(3): 11 - 14
- Kyle RA, Gertz MA, Witzig TE (2003) Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proc*;78:21-33
- Kyle RA(2004). Rajkumar SV: Multiple myeloma. *N Engl J Med*; 351 : 1860–1873
- Nau KC (2008). Lewis WD Multiple myeloma: diagnosis and treatment. *Am.Fam.Physician*;78(7):853-859.
- Oken MM, Creech RH, Tormey DC (1982). "Toxicity and response criteria of the Eastern Cooperative Oncology Group". *Am. J. Clin. Oncol.* ; 5 (6): 649–55.

- Omoti C, Halim NKD (2007). Plasma Cell Myeloma in a Tertiary Centre in Niger -Delta Region of Nigeria: Clinico-immunologic Analysis. *Pak. J. Med. Sci.* 23(1): 27-32.
- Omoti CE, Omuemu CE (2007). Multiple myeloma: a ten year study of survival and therapy in a developing nation. *JPMA*,57;341-344
- Papadaki H, Kyriakou D, Foudoulakis A, Markidou F, Alexandrakis M, Eliopoulos GD (1997) Serum levels of soluble IL-6 receptor in multiple myeloma as indicator of disease activity. *Acta Haematol* ; 97: 191 - 195
- Rajkumar SV, Kyle RA (2005). Conventional therapy and approach to management. *Best Practice and Research Clinical Haematology*; 18(4): 585 -601.
- Rajkumar SV, Kyle RA (2005). Multiple myeloma: Diagnosis and treatment. *Mayo Clin Proc*; 80 : 1371–1382
- Salawu L, Durosimi MA (2005). Myelomatosis: clinical and laboratory features in a Nigerians. *WAJM*: 24(1): 54 – 57
- San MJF, Garc'a- Sanz R (2005). Prognostic features of multiple myeloma. *Best Practice and Research Clinical Haematology*; 18(4) :569 – 583
- Soutar RL, Dawson AA, Wilson BJ (1996). Multiple myeloma in North East Scotland: a review of incidence and survival over three decades. *Health Bull. (Edinb)*; 54(3): 232-240.