
Original Article

Multiple myeloma: a ten year study of survival and therapy in a developing nation

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Abstract

Objective: To analyze the survival related to therapeutic modalities and haematological indices at presentation with outcome performed on records of all multiple myeloma (MM) patients'

Methods: A prospective study was conducted in the University of Benin Teaching Hospital, Nigeria from 1993 to 2003. Thirty patients were identified with diagnosis confirmed on the basis of atypical plasmacytosis (=30% in the bone marrow), monoclonal component in the serum or urine and radiological evidence of the typical skeletal lytic lesions.

Results: Males (n=20) outnumbered the females (n=10), with a median age of 54 years. The mean duration of survival of all patients was 7 months (median 3 months; $P < 0.0001$) with only 13.3% of the patients surviving at two years. The mean duration of survival of 10 patients on either therapy of vincristine, adriamycin, dexamethasone (VAD) or 8 patients on melphalan, prednisolone (MP) was 3 months, significantly shorter than 21 months for the 5 patients on a combination of both forms of therapy at different times (COMB) ($P = 0.0067$). The Kaplan-Meier estimates of survival showed survival probability was least in those without definitive therapy (NONE) as expected.

Conclusion: Late presentation and inadequate treatment from poor compliance with therapy in a setting of poverty and ignorance are suggested as factors contributing to the poor survival of the patients studied (JPMA 57:341:2007).

Introduction

Plasma cell dyscrasias are a group of disorders that arise from clonal proliferation of neoplastic plasma cells or associated B cells. Typically clinical manifestation varies as a result of the heterogenous biology spanning the entire spectrum from the early phase of indolent/smoldering myeloma to highly aggressive overt and terminal multiple myeloma (MM),¹ which is still incurable with the available treatment options.^{2,3} The occurrence of MM is worldwide and there is no doubt that the Negroid population and Afrocarribeans have a much larger share than the Caucasians, as also confirmed by the SEER data program.^{4,5} The decline in mortality and higher probability of survival for MM patients in the western world is due to recent advanced novel therapy protocol and wider use of the PCR-ASO (allele-specific oligonucleotide) designed to detect CDR3 sequence of the tumour/monitoring minimal residual disease.^{6,7} This is also coupled with the purging efficacy of the autologous blood stem cell transplants in

MM.^{8,9} However, these advanced management techniques are not readily available in most developing countries. Hence, the aim of this study was to analyze therapeutic modalities currently in use and determine the survival outcome of 30 patients managed for this condition in a tertiary health institution in a developing nation.

Patients and Methods

Between 1993 and 2003, 30 cases of MM patients consecutively seen at UBTH, a major referral center serving the South-South geopolitical region of Nigeria were studied. Clinicoimmunologic and demographic information of the patients including referrals and autopsy findings were noted. Pretreatment evaluation included complete clinical, radiologic skeletal survey and laboratory workup carried out at the center.

Diagnostic criteria, as recommended were based on clinical information, the presence of at least 30% atypical plasma cells on bone marrow examination (or biopsy of a tissue with monoclonal plasma cells), monoclonal proteins in the serum or urine with or without evidence of end-organ

damage.^{10,11} During the monthly cycle of treatment, patients were followed up for physical examination, blood count, renal and liver function tests. Bone marrow aspiration and biopsy with serum and urine electrophoresis were performed at intervals when patients' monoclonal components (MC) had reached maximum reduction. Overall duration of survival was estimated in all patients using simple percentage from the time of diagnosis/start of treatment to the date of death or the last follow up visit.

Table 1. Age distribution of multiple myeloma patients on presentation.

Age (years)	Frequency (%)
30-40	4 (13.3)
41-50	11 (36.7)
51-60	8 (26.7)
>60	7 (23.3)
Total	30 (100)

Table 2. The mean haematological indices in multiple myeloma patients at presentation and outcome at 1 year of therapy.

Parameters	Outcome		P-value
	Alive (n=10)	Dead (n=7)	
Haemoglobin (g/dl)	10.3 (± 2.7)	6.8 (± 0.6)	0.0031
Total leucocyte count ($\times 10^9/L$)	7.7 (± 2.8)	8.1 (± 3.9)	ns
Platelet count ($\times 10^9/L$)	241 (± 98)	108 (± 66)	0.0050
Erythrocyte sedimentation rate (mm/hr)	93.6 (± 47)	147 (± 8)	0.0065

ns: not significant.

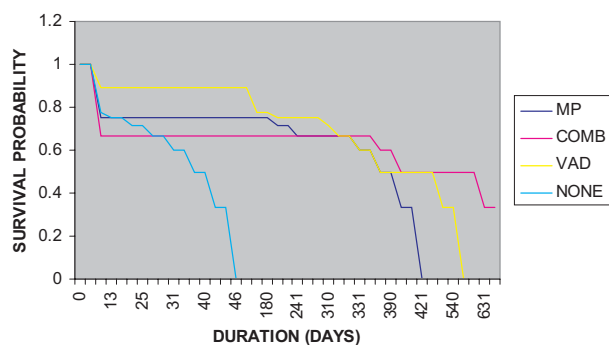


Figure 1. Kaplan-Meier estimates of survival of patients according to therapy. MP (Melphalan, Prednisolone); VAD (Vincristine, Adriamycin, Dexamethasone); COMB (MP and VAD); NONE (No therapy).

Instat package system was used to analyze the data obtained. The haematological indices were estimated using the Mann-Whitney and one-way analysis of variance (ANOVA) for significant association. Survival probability was estimated using the Kaplan Meier method.

Results

A total of 30 patients aged 34-75 years with an established diagnosis of MM, based on serum immunoelectrophoretic and clinical criteria over a ten-year period (1993-2003) were studied. The age-corrected male: female ratio of 2:1 indicated higher incidence of MM in males. The overall median age at presentation was 54 years with 13.3% of the patients less than 40 years (Table 1).

The haematological values at presentation were found to influence the outcome of survival after chemotherapy was started as shown in Table 2. We found a strong association between haemoglobin (Hb) and platelet count at presentation and 1 year survival in the myeloma patients ($P=0.0031$ and $P=0.005$ respectively). Also, the mean erythrocyte sedimentation rate (ESR) for the myeloma patients alive at 1 year was significantly lower than those that died within 1 year ($P=0.0065$). A positive correlation between Hb and platelet count at presentation was also obtained ($r=0.436$; $P=0.016$).

The Kaplan Meier estimates of survival probability for the four groups of patients (according to therapy) are displayed in figure. The chemotherapeutic regimen utilized were the standard single alkylating agent of MP administered to 26.7% of the patients, VAD administered to 33.3% of the patients and 5 cases (16.7%) who had initially MP and later switched to VAD after non-response of 3-4 months with one regimen. There was a trend for longer survival in the 5/23 patients given cycles of MP and later replaced with VAD when compared to the single regimens of either MP or VAD alone (median, 21 months vs 3 months; $P=0.0067$). Expectedly, the poorest survival recorded was in 23.3% (7/30) patients who had no form of therapy (NONE) due to financial constraint and other limiting factors. The mean duration of survival in the whole series was 7 months (median 3 months; $P<0.0001$) with a range of 1-96 months.

Response to chemotherapy is an independent factor associated with survival; and treatment results are analyzed on an intention to treat basis. Time to response was defined as the interval between treatment initiation and documentation of at least partial response (PR) i.e. $>50\%$ and $>90\%$ decrease of serum and urine MC level respectively. Complete response (CR) was defined as disappearance of the MC in serum and/or urine immunofixation, less than 5% plasma cells in the bone marrow and complete regression of extramedullary lesions if present. Patients who discontinued treatment for any reason before response assessment were considered as non-responders. Twenty-three patients who received chemotherapy had various outcome of response: CR was seen in 4 cases, PR in 12 cases and no response in 7 cases.

Discussion

There have been major advances in the treatment of MM in the past 20 years but for the individual patient the prognosis still remains uncertain. MM is seen in all races being the most prevalent blood cancer after non-Hodgkin's lymphoma.¹² It is said to account for 1% of all human cancers and 10% of all haematological malignancies.¹³ The occurrence of MM is worldwide but there are considerable differences in the recorded incidence and survival in different geographic areas.

The median age of 54 years at presentation revealed that our patients tend to present at much earlier age than elsewhere. For instance, the age of those referred to the Olmsted county and Mayo clinic, USA was 74 and 62 years respectively.^{14,15} We also found in this study that the mean duration of survival in the whole series was significantly low (7 months; $P < 0.0001$) in contrast to the longer duration experienced in the more developed economy.^{2,16,17} This survival outcome is poor when compared to the Western world as the 5 year survival could not even be estimated because most of the patients did not live up to this number of years or were lost to follow up. The survival in those with renal involvement in Northern India was reported to be only 4 months while those on dialysis was 6 months.¹⁸

Limited resources, illiteracy and ignorance led to late presentation and inability to begin and sustain treatment probably contributed to the short duration of survival. Patients resort to herbal and other unorthodox form of treatment before presentation. Missed diagnosis by health care providers in the primary and secondary health care facilities before referral also contributed to delay in diagnosis and onset of complications before presentation. These factors are similar to the studies in Senegal and other African literature¹⁹ and in China.²⁰ Our patients being on the younger side may probably have aggressive disease as shown with the various molecular biology of MM. Exposure to chemical substances and gas flares may be associated with an increased risk of MM implicating environmental factors as important aetiological/causal agent.^{21,22} This is because 83.3% of the patients reviewed were from the Niger Delta region of the country noted for its petrochemical industries and gas flare sites coupled with pollution of water from oil spillage. Logistics for providing blood and blood components is very difficult for most of the patients due to limited resources/financial constraint.

In spite of the advances recorded in the chemotherapeutic treatment of MM, the survival has only slightly improved. Reports from Western countries revealed that age, presence of complications and aetiological environmental factors were negative prognostic factors^{21,23} that were also present in our study with a high percentage

(13.3%) presenting at <40 years. Some of the complications presented were cord compression, protein deposition in visceral organ eg kidney and immunosuppression (infection). Presence of osteolytic bone destruction (pain), a hallmark of advanced myeloma was also reflected in clinical pathological fractures in 33.3% of the patients and 93.3% of the patients with haemoglobin $<10\text{g/dl}$. The probability of occurrence of anaemia due to cytokine production has been reported to depend on a number of variables which include the type, stage (Durie and Salmon)/duration of the malignancy, intensity of treatment protocol and the occurrence of intercurrent infection.²⁴ Environmental exposure to radiation or chemicals has been associated with increased myeloma.²⁵ Though there was no exposure to atomic/bomb or radiation, majority of the patients were from the Niger Delta Zone of Nigeria where there is exposure to chemical pollution. On the other hand, results of epidemiologic studies attempting to establish associations between myeloma and certain infections or autoimmune diseases are however inconclusive.²⁶ A considerable number of the patients presented with the expected haematological counts. Patients with a lower Hb and platelet count had a significantly lower remission rate with a poor outcome. This was shown in the strong association between the indices at presentation and 1 year survival ($P=0.0031$; $P=0.005$ respectively). Also, the mean ESR for the myeloma patients alive at 1 year was significantly lower than those that died within 1 year ($P=0.0065$).

The apparent longer duration of survival advantage of patients on MP and later VAD over either single regimen alone is not easily explained. However, it is possible that the myelosuppression due to MP may have wiped out most of the malignant cells. VAD on the other hand possibly continued to suppress mainly the malignant cells without myelosuppression, hence the apparent improved outcome. We had observed empirically that our younger patients (<60 years) on VAD tended to do better as time progressed than the older ones even though both groups occasionally presented with similar clinical and laboratory initial characteristics. This was also informed by the apparent pharmacological advantages of VAD over MP which include rapidity of response, lack of myelotoxicity and usefulness in patients with poor renal performance.²⁷ It has also been reported that VAD chemotherapy is a better initial option.²⁸ Therefore, the group of patients referred or previously on MP were switched to VAD including those with adverse effects/toxicity and those perceived to be doing poorly clinically, who did not respond after 3-4 months on MP. Those refractory to myelosuppressive doses of standard alkylating MP agent, VAD produced rapid and marked cytoreduction of over 75% in the treated patients by

improved response rate. This generally was associated with prolonged survival as has been previously reported.²⁹ Infact, it has been said that patients younger than 50 years seem to have a better prognosis when the observed survival rates are considered, but they showed an increased risk of death when the model takes into account the expected mortality of the underlying population. In all, data exist both to support and to refute the concept that patients who respond very quickly to induction therapy have a worse prognosis than those with a slower response.

In conclusion, the short duration of survival identified in our study compared to the western world can probably be best addressed by general measures targeted at reducing poverty, ignorance and health care reforms to reduce late presentation. Specific measure to ensure affordability and availability of drugs and laboratory support for monitoring these patients are needed. The high response rate with long lasting remission with VAD has again been confirmed to be a good combination therapy in MM patients when a more aggressive therapeutic approach than oral MP is warranted.

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