ORIGINAL ARTICLE

FACTORS AFFECTING OUTCOME OF PATIENTS WITH MULTIPLE MYELOMA

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Background: Multiple myeloma is a heterogeneous disease, with wide survival range and multiple risk factors and staging systems linked to survival. The objective of this study was to assess the overall survival of patients with multiple myeloma (MM) diagnosed and treated at Shaukat Khanum Memorial Cancer Hospital (SKMCH), Lahore with respect to various prognostic factors. **Methods:** This was a survival analysis with data collected retrospectively on 82 patients fulfilling the diagnostic criteria of multiple myeloma. Overall survival was studied in relation to International Staging System (ISS), renal failure (Serum creatinine >2 mg/dl), anaemia (Hemoglobin <10 mg/dl), bone involvement (presence of lytic lesion on skeletal survey) and hypercalcemia (serum calcium >11mg/dl) due to multiple myeloma at the time of diagnosis. **Results:** Mean age of patients was 61 years, including 67% males and 33% females. Median overall survival for ISS stage-I (24%), stage-II (44%) and stage-III (32%) was 58, 41 and 12 months respectively (p=0.01). Patients with renal impairment (16% of total) had median overall survival of 13 months compared to 41 months in patients without renal involvement (p=0.02). Hypercalcemia was noted in 27% patients with median overall survival of 32 months versus 38 months in patients without hypercalcemia, but its impact on survival was statistically insignificant (p=0.79). Similarly no significant impact on survival was noted in patients with bone involvement or anaemia found in 74 % and 38% of patient's respectively. **Conclusions:** ISS stage and renal failure due to multiple myeloma at presentation have a significant impact on survival. However, other prognostic factors like bone involvement, anaemia and hypercalcemia were not shown to influence survival significantly.

Keywords: Multiplemyeloma, survival, anaemia, hypercalcemia

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INTRODUCTION

Multiple myeloma (MM) is characterized by neoplastic proliferation of clonal plasma cells producing a monoclonal immunoglobulin. Multiple myeloma appears to start from transformation of post-germinal centre plasma cells into malignant cells.[1,2]Monoclonal gammopathy of undetermined significance (MGUS), a premalignant plasma cell proliferative disorder gives rise to MM in almost all cases.[3]MGUS progresses to symptomatic MM at a steady rate every year.[4] Multiple myeloma is the second most common form of haematological malignancy in the western world after non-Hodgkin lymphoma and it accounts for approximately 10% of haematological malignancies and 1% of all malignancies.[5]Clinical presentation is mostly with bone pains, anaemia, renal derangement, fatigue, weakness and hypercalcemia in descending order of frequency.[6]

The prognosis of multiple myeloma is based on tumour burden, as well as patient factors, nature of disease and how it responds to therapy.[7] Two of the most widely used staging systems of multiple myeloma include the Durie-Salmon staging system and the International Staging System (ISS). Durie-Salmon staging system is based on the measures of end organ damage (renal insufficiency, anaemia, hypercalcemia, lytic bony lesions) and immunoglobulin burden.[8] International staging system (ISS) was developed after a study done on more than 10,750 MM patients from over 17 institutions throughout the world. It divides disease burden into three stages based on serum albumin and beta-2 microglobulin levels as follows:[9] ISS stage I patients have serum beta 2 microglobulin levels <3.5 mg/L and serum albumin levels ≥3.5g/dl, ISS stage III comprises of patients with serum beta 2 microglobulin levels ≥5.5 mg/L, and ISS stage II includes patients who do not fall in either of the above mentioned group.

Anaemia, bone involvement, renal derangement and hypercalcemia are established adverse prognostic factors.[6]Low haemoglobin was strongly linked with adverse outcome in patients of multiple myeloma treated with autologous stem cell transplant.[10] Multiple factor contribute to renal impairment in myeloma patients.[11] Adverse outcome is directly linked to severity of renal derangement in multiple myeloma patients.[12]

In our study, we tried to find out the impact of ISS stage on the outcome of patient with multiple myeloma treated at our institution. We also looked at

the relationship of renal failure, hypercalcemia, and anaemia and bone involvement at the time of diagnosis with survival.

MATERIAL AND METHODS

This was a survival analysis with data retrospectively collected on 82 Multiple myeloma patients diagnosed and treated at Shaukat Khanum Memorial Cancer Hospital, Lahore from 2001 to 2010. Multiple Myeloma was defined according to International myeloma working group (IMWG)as follows:[13,14]
All three criteria must be met:

- Presence of a serum or urinary monoclonal protein,
- Presence of clonal plasma cells in bone marrow or a plasmacytoma,
- Presence of end organ damage felt related to the plasma cell dyscrasia, increased serum calcium, Lyticbone lesions, Anaemia or Renal failure.

All patients aged 18 and above, fulfilling the above mentioned diagnostic criteria were included in the study. Patients who were noncompliant or had significant comorbidities like advanced heart failure, decompensated liver disease or advanced lung diseases were excluded. This study was conducted after approval from Hospital's Institutional Review Board.

The length of time from the date of diagnosis of disease, to the time when half of the patients were still alive was taken as median overall survival. Median overall survival was studied in relation to International Staging System (ISS), renal impairment due to multiple myeloma, anaemia, bone involvement and hypercalcemia present at the time of diagnosis. Patient with serum creatinine levels >2 mg/dl were categorized as having renal impairment. Bone involvement was defined as presence of lytic lesions on skeletal survey. Patients with Haemoglobin of <10 g/dl were taken as having anaemia and patients found to have serum calcium greater than 11mg/dl were considered to havehypercalcemia. Survival data was studied irrespective of treatment regimenused.

Data were collected through a *pro forma* from hospital electronic database. Patient date of registration at our hospital was noted and also the date at which he was last time seen at our hospital, and date of death was noted for patients who had passed away. Patients who lost follow up with our hospital were contacted on phone to note their current status whether dead or alive. Haemoglobin, serum calcium level, presence of lytic lesions on skeletal survey and serum creatinine value were noted at first presentation and patients were grouped accordingly whether anaemia, hypercalcemia, bone involvement or renal derangement was present or not at presentation. Data were analysed using SPSS-19. Median overall survival was studied using Kaplan Meier survival analysis using log rank test to find out which risk factors present at initial presentation lead to poor outcome. *p*-value less than 0.05 was taken as statistically significant.

RESULTS

Total number of patients was 82, out of which 55 (67%) were male and 27 (33%) female. Median age of patients was 61 years (range 35–78 years).Median follow-up was 75 months. Patients were divided according to ISS stage into three categories. Twenty (24%) patients were with ISS stage I, 36 (44%) patients with Stage-II and 26(36%) patients were with ISS stage-III. Patients with stage-I had median survival of 58 months compared to 41 months for stage-II and 12 months for stage-III (p=0.001), (Figure-1).

Renal derangement was documented in 16% patients at the time of diagnosis with median survival of 13 months. Patients with normal renal function at presentation fared significantly better with median survival of 41 months (p=0.02). At presentation 38% patients were found to have low haemoglobin. Median overall survival was worse for patients with anaemia, 39 months versus 34 months for patients without anaemia but the difference was not statistically significant (p=0.43) as shown in table-1.

Bone involvement was found in 61 patients out of total 82 patients. Patients without bone disease did better with median overall survival of 44 months compared to patients with bone disease having median overall survival of 33 months(p=0.12).Hypercalcemia was found in 22 % of patients and it did not lead to poorer outcome. Median overall survival of patients with hypercalcemiawas 32 months, compared to 38 months in patients without hypercalcemia (p= 0.79).

Table-1: Median overall survival of patients based on anaemia, bone involvement, renal derangement and hypercalcemia at presentation

	Anaemia		Bone Involvement		Renal Derangement		Hypercalcemia	
	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Median survival in months	39	34	33	44	13	41	32	38
***p*-value**	0.43		0.12		0.02*		0.79	

*statistically significant

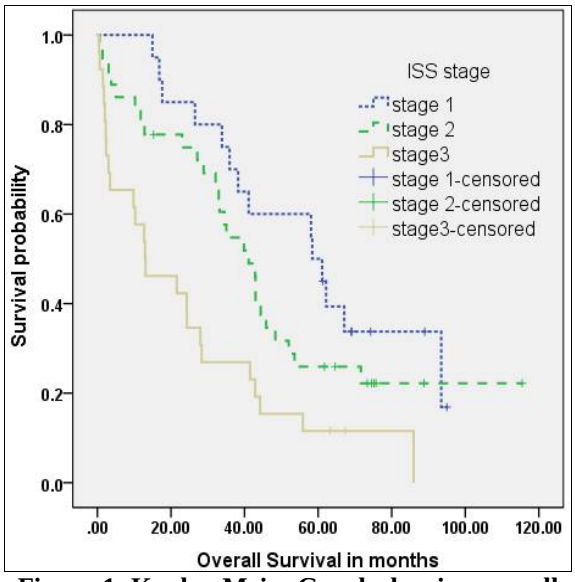

Figure-1: Kaplan Meier Graph showing overall survival in months based on ISS stage (*p*= 0.001)

DISCUSSION

Multiple myeloma is a heterogeneous disease, with wide survival range and multiple risk factors and staging systems linked to survival. Survival is higher in younger people and lower in the elderly.[15] C-reactive protein (CRP) and beta-2 microglobulin (which is an expression of tumour burden) has been used to predict survival.[16] A study by Larsen *et al* found that a significant reduction in plasma cell proliferation in patients with newly diagnosed MM is an important predictor of survival.[17]

A large multicentre study done in 2005, which led the foundation of ISS staging system, showed median overall survival for patients with ISS stages-I, II, and III: 62, 44, and 29 months, respectively.[9] The impact of ISS staging system on survival was also demonstrated in subsequent Asian data.[18] In our study, median survival of ISS stage-I and II patients is somewhat comparable to above mentioned international survival figures but the survival is worse for stage-III. Renal impairment at presentation led to poor outcome in multiple myeloma patients as established from data of previous study.[6] Other factors like hypercalcemia, anaemia and bone involvement though known to be associated with adverse prognosis[6], did not seem to impact survival significantly in our patients probably due to small sample size. All patients included in our study were treated with Thal/Dexa (Thalidomide and Dexamethasone) or MP (Melphalan and Prednisolone) chemotherapy regimens.

A relatively oldstudyfromIndia showed median survival of 30 months in myeloma patients. All these patients were treated with melphalan and prednisolone.[19] In a more recent regional study conducted on multiple myeloma patients treated with autologous stem cell transplant median overall survival has improved to 79 months.[20] Survival data was not segregated according to ISS stage in any of these studies. A similar study from China showed improvement in median survival demonstrated in all stages of MM according to ISS staging system treated with newer agents and autologous stem cell transplant.[21]

In our study survival is obviously inferior to patients treated with autologous stem cell transplant as expected. Another important contributing factor is that none of our patients was treated with newer immune-modulator drugs like Bortezomib and Lenalidomide. Lack of public awareness and poor socioeconomic conditions hinder early diagnosis of this condition leading to poor outcome. Availability of newer immune-modulator drugs and autologous stem cell transplant can improve the survival of our patients. We also need to create awareness in our population about this disease in order to diagnose these patients at an earlier stage.

CONCLUSIONS

In this study survival was effected by ISS stage that corresponded with established data. Renal impairment was also documented to effect survival but other risk factors like anaemia, hypercalcemia and bone involvement failed to make an impact on survival in our population. We need further studies to explain the impact of these variables in future.

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