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International Staging System: A Tool to Predict Survival in Patients with Multiple Myeloma

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Abstract: This descriptive case series study was evaluates the International Staging System (ISS) for the prediction of survival in patients with multiple myeloma and was conducted in the department of Medicine at Liaquat University Hospital from June 2009 to June 2011. All patients above 12 years of age, of either gender with history of bone pain, usually in the back and ribs broken bones, usually in the spine, feeling weak and very tired, feeling very thirsty, frequent infections and fevers, weight loss, nausea, constipation and frequent urination were further evaluated for multiple myeloma. The widely accepted schema for the diagnosis of multiple myeloma uses particular combinations of laboratory, imaging and procedure findings, while the International Staging System for multiple myeloma was used for staging or prognosis purpose and the survival was measured from the onset of nonradiation therapy to time of death or last contact. During study period total 23 patients of multiple myeloma were evaluated for staging and prognosis by International Staging System. Of twenty three 16 (70%) were males and 07 (30) were females. The overall mean age was 62.78± 8.86 (SD) years while the mean age in male and female population was 56.82 ± 10.65 (SD) and 60.77 ±7.76 (SD) respectively. The mean haemoglobin, creatinine and calcium were 7.56±2.98 g/dl, 3.44±1.24 mg/dl and 13.72±3.88 mg/dl respectively. The male and female distribution in relation to International Staging System was 04(25.0%) and 01 (14.3%) in stage I, 04(25.0%) and 02(28.6%) in stage II while 08(50.0%) and 04 (57.1%) in stage III. The median survival in relation to International Staging System was 36.4 months in 05(22%) stage I patients, 20.6 months in 06(26%) stage II patients and 10.8 in 12(52%) stage III patients. the ISS has better reliability, simplicity and predictability for survival of patients with multiple myeloma.

Key words: Multiple Myeloma · Staging · ISS · Plasmacytoma

INTRODUCTION

Multiple myeloma also known as plasma cell myeloma or Kahler's disease is a cancer of plasma cells, a type of white blood cell normally responsible for the production of antibodies and accounts for approximately 10% of hematologic malignancies [1, 2]. The annual incidence, age-adjusted to the 2000 US population, is 4.3 cases per 100,000 people, resulting in more than 15,000 new patients in the United States each year [3, 4]. Multiple myeloma is twice as common in African Americans as in white persons and is slightly more common in men than in women. The median age at onset is 66 years and only 2% of patients are younger than 40 years at diagnosis [5]. The plasma cell proliferation usually results in extensive skeletal destruction with osteolytic lesions, hypercalcemia, anemia and, occasionally, plasma cell infiltration in different organs. The excessive production of a monoclonal (M) protein can lead to renal failure, hyperviscosity syndrome or recurrent bacterial infections. [6]

The combinations of prognostic factors were suggested for staging classification of myeloma patients [7]. In 1975, Durie and Salmon [8] introduced a staging system, the Durie/Salmon (DS) system, using commonly available clinical parameters that predicted myeloma cell

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Table 1: Diagnostic considerations for multiple myeloma

I	Plasmacytoma on tissue biopsy
II	Bone marrow with greater than 30% plasma cells
III	Monoclonal globulin spike on serum protein electrophoresis, with an immunoglobulin (Ig) G peak of greater than 3.5 g/dL or an IgA peak of greater than 2 g/dL, or urine protein electrophoresis (in the presence of amyloidosis) result of greater than 1 g/24 h
	(a) Bone marrow with 10-30% plasma cells
	(b) Monoclonal globulin spike present but less than category III
	(c) Lytic bone lesions
	(d) Residual IgM level less than 50 mg/dL, IgA level less than 100 mg/dL, or IgG level less than 600 mg/dL
The following combinations of findings are used to make the diagnosis of multiple myeloma:	
I plus b, c, or d	
II plus b, c, or d	
III plus a, c, or d	
a plus b plus c	
a plus b plus d	

Table 2: The international staging system for multiple myeloma

STAGE	
I	Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/dl)
II	Neither stage I or III, meaning that either: (a) The beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level), OR (b) The albumin is below 3.5 while the beta-2 microglobulin is less than 3.5
III	Serum beta-2 microglobulin is greater than 5.5.

tumor burden. Factors in the DS classification included the level and type of monoclonal protein, hemoglobin, calcium level and number of bone lesions. Creatinine level (substage A: serum creatinine <2 mg/dL; and substage B: serum creatinine =2 mg/dL) further defined lower versus higher risk patients in each of the three tumor mass stages. However, this staging system has limitations, especially in the categorization of bone lesions [9, 10]. Recently, Greipp *et al* [11] have developed the new International Staging System (ISS), a collaborative effort by investigators from 17 institutions worldwide and data on 11,171 patients. The ISS overcomes the limitations of the Durie- Salmon staging and divides patients into 3 distinct stages and prognostic groups solely on the basis of serum β2- microglobulin and albumin levels. The stage of the disease at presentation is a strong determinant of survival, but it has little influence on the choice of therapy since almost all patients, except for rare patients with solitary bone tumors or extramedullary plasmacytomas, have generalized disease. By considering such literature in mind the present study was conducted to evaluate the prognosis of patients with multiple myeloma by International Staging System at tertiary care teaching hospital Hyderabad / Jamshoro.

MATERIALS AND METHODS

This descriptive case series study was conducted in the department of Medicine at Liaquat University Hospital from June 2009 to June 2011. All patients above 12 years of age, of either gender with history of bone pain, usually in the back and ribs broken bones, usually in the spine, feeling weak and very tired, feeling very thirsty, frequent infections and fevers, weight loss, nausea, constipation and frequent urination through outdoor patient department (OPD), casualty outdoor department (COD) or admitted in medical unit were evaluated and enrolled in the study. The detailed history of all such patients was taken and complete physical and relevant clinical examination was performed. All the routine and specific investigation including complete blood count (to determine if patient has anemia, leucopenia or thrombocytopenia), bone marrow aspiration for cytology and cytogenetics, a comprehensive metabolic profile including urea/creatinine, uric acid, protein and globulin levels, serum protein electrophoresis for M band, Beta 2 microglobulins and c-reactive proteins, Imaging studies including serial skeletal X-Rays for osteopenia or lytic lesions. MRI (magnetic resonance Imaging) and PET (positron emmision tomography), serum protein electrophoresis is performed for level and type of M-protein, creatinine, lactate dehydrogenase (LDH), serum albumin and β_2M. The widely accepted schema for the diagnosis of multiple myeloma (MM) uses particular combinations of laboratory, imaging and procedure findings as diagnostic criteria. (Table 1). The International Staging System for multiple myeloma was used for staging or prognosis

purpose (Table 2) and the survival was measured from the onset of nonradiation therapy to time of death or last contact. The known / diagnosed cases of multiple myeloma were also included in the study. The informed consent was taken from every patient or from attendants of p a tients after full explanation of procedure regarding the study and all such maneuvers was performed under medical ethics and through the cooperation of whole research team. For recruitment of the subjects the non - probability purposive technique was used while the exclusion criteria of the study were; conditions associated with an increased rate of cell production or destruction, severe infections, viral infections such as CMV (cytomegalovirus) and some conditions that activate the immune system, such as inflammatory conditions and autoimmune disorders that increases the β_2M levels, the drugs such as lithium, cyclosporine, cisplatin, carboplatin and aminoglycoside antibiotics can increase β_2M blood and / or urine concentrations. Recent nuclear medicine procedures and radiographic contrast media can affect test results, malignant Lymphoma, metastatic carcinoma; monoclonal gammopathies of uncertain origin and waldenstrom hypergammaglobulinemia. The data was collected on pre-designed proforma and analyzed in SPSS version 10.00. The frequency and percentage was calculated for gender distribution. Mean ±SD was computed for quantitative variables like age and duration of illness. The stratification was done on age, gender and stage of disease.

RESULTS

During study period total 23 patients of multiple myeloma were evaluated for staging and prognosis by International Staging System. Of twenty three 16 (70%) were males and 07 (30) were females. The overall mean age was 62.78±8.86 (SD) years while the mean age in male and female population was 56.82±10.65 (SD) and 60.77±7.76 (SD) respectively. The mean haemoglobin, creatinine and calcium were 7.56±2.98 g/dl, 3.44±1.24 mg/dl and 13.72±3.88 mg/dl respectively. The symptoms observed were bone pain 18(78%), weakness and very tired 20(86%), feeling very thirsty 15 (65%), frequent infections and fevers (20 (86%), weight loss 22 (96%), nausea 19 (83%), constipation 13 (56%) and frequent urination 11 (48%). The mean beta-2 microglobulin and albumin in overall patients was 5.99±1.70 mg/dl and 3.24±1.09 g/dl. The International Staging System in relation to gender distribution and median survival is shown in Table 3-4 .

Table 3: Gender distribution in relation to International Staging System

	Gender		
Stage	Male	Female	Total
I	04(25.0%)	01 (14.3%)	05(21.7%)
II	04(25.0%)	02(28.6%)	06(26.1%)
III	08(50.0%)	04 (57.1%)	12(52.2%)
Total	16(100%)	07(100%)	23(100%)

Table 4: Median Survival in Relation to International Staging System

Stage	*n* = 23 (%)	Median survival (months)
I	05(22%)	36.4
II	06(26%)	20.6
III	12(52%)	10.8

DISCUSSION

Determining the prognostic factors of multiple myeloma is important for predicting disease outcome and determining the treatment method. Up till yet, a number of prognostic factors have been identified including hemoglobin, calcium, creatinine, β2-microglobulin [12, 13], albumin [14], C-reactive protein [15], the plasma cell labeling index [16] and chromosomal 13 deletion or other chromosomal abnormalities. [17] Among these, β2-microglobulin has been the single most important prognostic factor for predicting survival and it is correlated with the tumor burden and renal function. The serum albumin may reflect the liver function and the nutritional status. In present study the mean age was 62.78± 8.86 whereas it was 60.83± 12.73 years in the study published in 2007. [18] The specific cause of decreased albumin in some multiple myeloma patients is not certain; however, a lower albumin may reflect effects on the liver by interleukin-6 produced by the microenvironment of myeloma cells. The strong correlations between serum levels of Sß2M and serum albumin and myeloma patient survival imply connections to important underlying mechanisms. There are several clues in the published literature, [19, 20] but to date, the underlying biology remains to be explored. Because the levels of Sß$_2$M and albumin are now specified by the ISS, it is critical that laboratory variation be minimized by standardizing methods used to determine their levels, specifically in multiple myeloma. In present study the median survival observed is 36.4, 20.6 and 10.8 months whereas it was 62, 44 and 29 months in the study by Choi [18]

It was recently published that the ISS systems at the time of diagnosis can predict the prognosis of multiple myeloma patients who have undergone high dose chemotherapy with autologous peripheral stem cell transplantation as a first-line therapy [21]. Furthermore, it was also published that the overall survival could be predicted by the the ISS but not by the DS staging system. One study that evaluated the significance of five staging systems in 470 multiple myeloma patients showed the superiority of the ISS over the DS staging system and the other prognostic classifications based on a combination of β2-microglobulin and albumin. [22] It is unclear whether higher ISS stages reflect higher myeloma tumor burden / aggressiveness or the level of target organ damage or both. Patients with a high ISS stage are at higher risk of early death, but it is unclear whether this reflects an inability to receive and tolerate aggressive therapy or myeloma biology or both. A smaller study [21] found that the ISS was better correlated with post transplant outcomes than the DSS. Regarding clinical presentation and haematological manifestation the present study is consistent with the study published in 2005 and 2010 [23, 24]

It is identified that the ISS staging system is broadly useful and that it will provide a sound base for more advanced studies in the future, it is also suggested that the ISS might be a more reliable and simple staging system for multiple myeloma patients.

CONCLUSION

Our study showed that the International Staging System has better reliability, simplicity and predictability for survival of patients with multiple myeloma.

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