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Age of Onset of Multiple Myeloma: A Paradigm Shift in Indian Patients

KEYWORDS: myeloma, age, multiple myeloma

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ABSTRACT *Multiple Myeloma (MM) is a clonal disorder of plasma cells with age having a major impact on treatment plan and outcome. While young patients are transplant eligible, tolerate therapy well and have better outcome, older patients are intolerant to intense therapy. Young age of onset also reflects an early exposure to inciting factors triggering myeloma. A retrospective analysis of patients diagnosed with Multiple Myeloma in our institution from January 2010 to December 2015 is performed. A total of 302 patients are diagnosed with MM as per International Myeloma Working Group (IMWG) Criteria in this period. Median age of diagnosis is 54years, range being 28-84years. Age of onset of Myeloma in Indian patients is a decade earlier compared to the West. Further studies to understand the triggering factors for early onset of MM in Indian patients are warranted.*

Introduction

Multiple Myeloma (MM) is clonal disorder of plasma cells. Age has a major impact on the treatment and outcomes in multiple myeloma. Younger patients present with more favourable features, can tolerate more intensive therapy and their survival is better than older patients. Median survival is 5 to 7 years in patients treated with high-dose chemotherapy and autologous transplantation and 3 to 4 years in patients treated with conventional chemotherapy.[1] The majority of patients treated with high-dose therapy and autologous transplantation are younger than 65 years old, whereas patients treated with conventional therapy are usually older than age 65.

Multiple Myeloma is classically described as a disease of elderly population, with a median age at manifestation of approximately 70 years in the United States[2] and 72 years in Europe.[3] All Oncology textbooks quote myeloma as a disease of elderly but Indian scenario is different. In India, median age of onset is much lower compared to the West.

Since age has an important role in treatment decision in myeloma ultimately affecting the outcome and also indicates early exposure to inciting factors, we studied the age of onset of MM in our institution.

Patients and Methods

A retrospective analysis of patients diagnosed with Multiple Myeloma in our institution from January 2010 to December 2015 is performed. This includes all the inpatients and outpatients.

International Myeloma Working Group (IMWG) Criteria are used for the diagnosis of Multiple Myeloma. These include clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features.

Hypercalcemia: serum calcium >0.25 mmol/L (>1mg/dl) higher than the upper limit of normal or >2.75 mmol/L (>11mg/dl)

Renal insufficiency: creatinine clearance <40 ml per minute or serum creatinine >177μmol/L (>2mg/dl)

Anemia: hemoglobin value of >20g/L below the lowest limit of normal, or a hemoglobin value <100g/L

Bone lesions: one or more osteolytic lesion on skeletal radiography, CT, or PET/CT. If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

The revised IMWG criteria (2015) allow, in addition to the classic CRAB features, three "myeloma defining events" (MDEs). The presence of at least one of these markers is considered sufficient for a diagnosis of multiple myeloma, regardless of the presence or absence of symptoms or CRAB features.

60% or greater clonal plasma cells on bone marrow examination

Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L (a patient's "involved" free light chain—either kappa or lambda—is the one that is above the normal reference range; the "uninvolved" free light chain is the one that is typically in, or below, the normal range)

More than one focal lesion on MRI that is at least 5mm or greater in size.

Results

A total of 302 patients were diagnosed with MM in the study period. Of the 302, 121 patients (40%) are less than 50years and 181 patients (60%) are more than 50years. Numbers of patients are 4, 36, 87, 88, 59, 25 and 3 in age groups 21-30, 31-40, 41-50, 51-60, 61-70, 71-80 and more than 80years respectively. Median age is 54 years, range 28 to 84 years.

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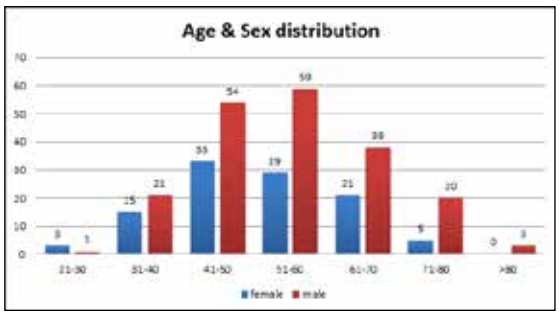


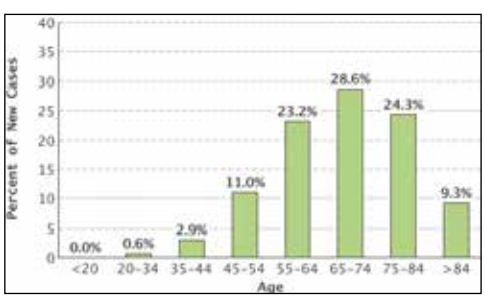
Figure 1: Age and Sex distribution in the study

Discussion

The age of onset of MM in Indian population differs sharply from other countries. Though exact Indian statistics are lacking, available data from hospital registries and publications clearly show a paradigm shift in age of onset of MM in Indian population.

All the Western data suggest age of onset as 7th or 8th decade while the data from India suggest 6th decade as age of onset.

As per the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute which provides information on cancer statistics in the United States, MM represents 1.8% of all new cases in 2016.



SEER 18 2009-2013, All Races, Both Sexes

Figure 2: Age distribution in SEER data

As per SEER, Myeloma is most frequently diagnosed among people aged 65-74 with the median age at diagnosis being 69years.

As per Cancer research UK, Myeloma incidence is strongly related to age, with the highest incidence rates being in older males and females. In the UK in 2011-2013, on average each year around 6 in 10 (59%) cases were diagnosed in people aged 70 and over.[4-7]

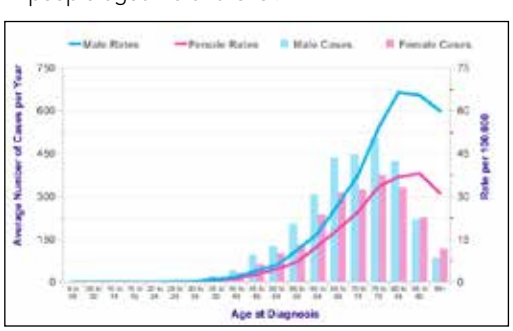


Figure 3: Age distribution, UK patients

Turesson. I et al studied the patterns of MM from 1950 to 2005 in Sweden. Between 1950-1959 and 2000-2005, the median age at diagnosis of MM increased from 70 to 74 years, and the proportion of newly diagnosed patients aged 80 years or older increased from 16% to 31%.[8]

A study by Pragnya et al from the our institution from January 2008 to December 2011 showed a mean age 52 years with a range of 32-70 years.[9]

The median age is 55years in the study by R. Subrahmanian et al from JIPMER, [10] and 55years in the study **Erukkambattu Jayashankar.11**

Nair MK et al reviewed Case records of 142 patients with multiple myeloma treated at the Regional Cancer Centre, Trivandrum, between 1984 and 1989. The mean age of the patients was 61 years in their study.[12]

Early age of onset in Indian patients means early exposure to inciting agents triggering MM. Exposure to ionizing radiation is the strongest single risk factor linked to an increased risk of multiple myeloma. People exposed to low levels of radiation also demonstrate an increased incidence of myeloma, including radiologists, employees in the nuclear industry, or those handling radioactive materials. An association between exposure to various chemicals and the increased risk of myeloma remains ill defined. Exposure to metals, especially nickel; agricultural chemicals; benzene and petroleum products; other aromatic hydrocarbons; agent orange; and silicon have been considered as potential risk factors. Among medications, only mineral oil used as laxative has been reported to be associated with an increased risk of MM in some patients.[13]

Hereditary and genetic factors may predispose patients to myeloma development. However, direct genetic linkage has not been established.[13]

Although epidemiologic studies have not been able to conclusively establish an association between MM and infectious or autoimmune diseases, a recent retrospective cohort study in US veterans demonstrated significantly risks of MM in patients with a history of autoimmune, infectious, and inflammatory disorders. These results indicate that various types of immune mediated conditions might act as triggers for MM development. [13]

India is a developing country with high childhood infection rate. Also agriculture is the backbone of India and there is an increasing use of insecticides and pesticides by the agricultural workers without proper precautions. There is no proper health education for the workers in various chemical industries. Low literacy rate and high levels of ignorance are contributing to undue exposure to various infections and chemicals. Early exposure to these agents might possibly play a role for early age of onset of MM in Indian population.

Conclusions

Age of onset of Myeloma in Indian patients is a decade earlier compared to the West. Further studies to understand the triggering factors for early onset in Indian patients are warranted.

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