Epidemiology, Biology, and Outcome in Multiple Myeloma Patients in different Geographical Areas of the World

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Date of submission
November 1st, 2011
Date of acceptance
December 5th, 2011
Available online
January 25th, 2012

Keywords
multiple myeloma, ethnicities, epidemiology, outcome, ASCT

Citation
Saraf S, Patel P, Rondelli D. Epidemiology, Biology, and Outcome in Multiple Myeloma Patients in different Geographical Areas of the World. Journal of Advances in Internal Medicine. 2012;01(1)20-32.

ABSTRACT

Multiple myeloma has an incidence rate of 102,000 and death rate of 72,000 people per year worldwide. The incidence varies by ethnicity with highest rates observed in African Americans followed by people from industrialized nations. Consistent risk factors for MM include increasing age, male gender, black race, MGUS, and family history with familial aggregates seen globally. Chromosome abnormalities commonly seen include hyperdiploidy, translocations involving the immunoglobulin heavy chain, monosomy of chromosome 13, gains of chromosome 1q, and deletion of 17p. These chromosome abnormalities have also been observed in Asian and South American countries, although mild variability in frequencies has been seen. The International Staging System (ISS) was first validated in MM patients from North America and Europe and has shown significant correlation to survival in cohorts from South America and Asia. High-dose chemotherapy followed by autologous stem cell transplant (ASCT) and the novel agents, thalidomide, lenalidomide, and bortezomib are recent advances that have improved response rates and survival. The original studies proving efficacy were primarily performed in the United States and European countries. Although, African Americans were seen to be 23% less likely to receive chemotherapy, similar response rates and survival were seen when given equal access to care. Recent data from several countries in South America and Asia have also shown similar advances in response rates and survival to ASCT and novel agents. The parallel improvements signify that monitoring adequate and equal access to care is critically important in order to improve the long term outcome of MM globally.

INTRODUCTION

Multiple myeloma (MM) is a plasma cell malignancy that can present with heterogeneous clinical manifestations and can affect different tissues and organs. Therefore, besides hematology/oncologists that are usually primary care givers of MM patients, general medicine or family practice physicians as well as multiple medical specialists, such as nephrologists, endocrinologists, cardiologists and radiation oncologists are frequently involved. In addition, since the age of onset can vary but more often is within the fifth and sixth decade, therapeutic options encompass aggressive treatments but also safer palliative therapies, that can be necessary in the presence of other co-morbidities.

In this review we analyzed the epidemiology, biology and clinical outcome of MM patients as reported by investigators in different areas of the world. Specific aspects that are raised in this work are possible biologic differences among ethnicities, as suggested for example by the an increased incidence of MM in African American (AA) patients, as well as possible differences in the outcome due to environmental or access to care systems throughout the world.

EPIDEMIOLOGY

Multiple myeloma (MM) is characterized by clonal proliferation of malignant plasma cells which produce monoclonal proteins and can result in bone lesions, renal damage, hypercalcemia, increased susceptibility to infections and/or cytopenias. Worldwide, approximately 102,000 new cases of MM are diagnosed representing 0.8% of all cancer diagnoses and 72,000 patients will die from MM accounting for 1.0% of all cancer deaths per year.[1] Although not well understood, the incidence and mortality appears highest in industrialized nations including North America, Australia/New Zealand, and Europe and the incidence appears to be rising in these regions while remaining relatively stable in Asian countries (Figure 1).[2]
African Americans (AA) have the highest incidence of MM which is approximately double what is seen in other ethnicities.[3] Similar patterns of incidence and mortality to their areas of origin have been observed in Arab Americans that have migrated to the metropolitan Detroit area and Asians that migrated to California suggesting that environmental factors may play less of a role in the etiology of MM.[4, 5]

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Table 1. **Risk factors associated with risk of progression of monoclonal gammopathy of undetermined significance to multiple myeloma after 20 years of follow up[19]**

MGUS Risk Factors	Number of Risk Factors Present	Risk of Progressing to multiple myeloma at 20 years
- Elevated M-protein (defined as > 1.5mg/dL)	3 Risk Factors	58%
- IgA or IgM MGUS	2 Risk Factors	37%
- Abnormal serum free-light chain ratio	1 Risk Factors	21%
	No Risk Factors	5%

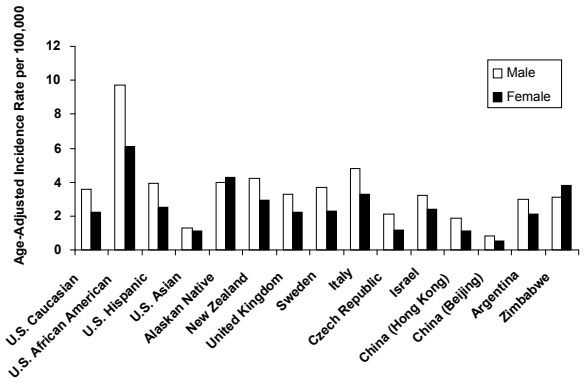

Figure 1. **Multiple myeloma global age-adjusted incidence rates per 100,000 people for men and women[12]**

Monoclonal gammopathy of undetermined significance (MGUS) is considered a precursor to MM and is defined as the presence of a monoclonal protein without evidence of organ damage. The prevalence of MGUS also varies by ethnicity with the highest rates seen in African Americans and in Ghanian men.[6, 7] According to studies screening similar age groups, worldwide estimates of the prevalence of MGUS are 5.8% in Ghana, 3.2% in American Caucasians, 2.4% in Japan, and 1.7% in France.[8-11]

RISK FACTORS

Although consistent differences in incidence and mortality among varying ethnicities have been observed, the etiologies for these patterns are unclear. The currently accepted risk factors for MM include increasing age, male gender, black race, positive family history and MGUS with additional possible risk factors including obesity, low fish consumption, low green vegetable consumption, AIDS, and Herpes Zoster infection.[12]

Data from the SEER database has shown that approximately 99% of new MM cases are over the age of 40 years at the time of diagnosis and there has been consistent data showing a rise in the incidence rate with age, peaking between age 80-84.[3,13] Similarly, these large databases have consistently shown higher rates of MM in males and African Americans.

Patients with MGUS have also been shown to have a higher risk of MM in several studies. In the Mayo Clinic study, a cohort of 1,384 patients diagnosed with MGUS were followed prospectively from 1960 to 1994. The overall risk of progressing to MM was 1% per year, 39% of patients developed MM within 25 years of follow up, and the relative risk of progression in patients with MGUS to multiple myeloma was 25 (95% CI 20.0 – 32.0).[14] Similar relative risk and patterns of progression to MM have been seen in MGUS patients from Denmark (RR 34.3, 95% CI 24.8-46.2), Iceland (10% progression over 3.8 years), and Italy (31.3% progression over 20 years).[15-17] Although AA have a higher prevalence of MGUS, their rates of progression to MM do not appear to be higher. In the Veterans Affairs Hospital study by Landgren et al, similar rates of progression to MM were observed between AA (17%) and Caucasians (15%) by 10 years of follow up.[18] Although there are no confirmed features that determine which patients with MGUS will progress to MM, a stratification model for risk of progression was developed using data from the Mayo Clinic cohort.[19] Increasing M-protein levels were associated with higher risks of progressing to MM by 20 years: 14% for < 0.5mg/dL, 16% for 1.0mg/dL, 25% for 1.5mg/dL, 41% for 2.0mg/dL, 49% for 2.5mg/dL, and 64% for 3.0mg/dL. Patients with either an IgM or IgA isotype were also at higher risk for progressing when compared to patients with the IgG isotype (p=0.001). Patients with an abnormal serum free light-chain ratio had a higher risk of progressing to MM in comparison to patients with a normal ratio (p<0.001). A stratification model using these three risk factors found that patients with all three risk factors had a 58% risk of progression, two risk factors had a 37% risk, one risk factor had a risk of 21%, and patients with none of the risk factors had a 5% risk of progression at 20 years (Table 1).

There have been several studies that have shown higher risks of MM in people who have a family history of MM, especially in first degree relatives. The risk of MM was estimated at 2.33 (95% CI: 1.12-4.26) in first degree relatives of 218 cases of MM in Iceland.[20] Similarly, increased risks in first degree relatives were observed in 8,406 cases of MM in Sweden (RR 1.67, 95% CI 1.02-2.73).[21] The data is less conclusive with regards to the risk of MM in people with a family history of MGUS or in people with second or third degree relatives with a history of MM.[19, 20] Familial aggregates have been reported in Caucasian American, African American, Italian, French, Turkish, and Mexican families.[22-27] In a study of five families where the parent and the child develop MM, it was observed that the offspring had a significantly younger median age of presentation (71 years in the parent vs. 50 years for the child; p<0.0001).[28] In an attempt to identify potential inheritable risk factors for MM, investigators have performed HLA typing. The HLA alleles identified to be high risk for AA included Bw65, Cw2, and DRw14 and for Caucasians included A3 and Cw2.[29] The HLA Cw2 allele was a risk factor for both AA (RR 5.7, 95%CI 1.5-26.6) and Caucasians (RR of 5.7 (95% CI: 1.5-26.6) and

Table 2. **Risk stratification of multiple myeloma based on cytogenetic abnormalities[51]**

Risk Category	Cytogenetic Abnormalities
Standard-Risk	1. Hyperdiploidy 2. t(11;14) 3. t(6;14)
High-Risk	1. 17p deletion 2. t(4;14) 3. t(14:16) 4. t(14;20) 5. Deletion of chromosome 13 or hypodiploidy by conventional karyotyping

2.6 (95% CI: 1.0-7.2) and were present in equal frequency in AA and Caucasian controls. Another potential inherited HLA antigen seen in higher frequency in AA with MM is the HLA-Cw5.[30] A negative risk for MM was observed with inheritance of the HLA-Aw32 allele in French Caucasians.[31] Carriers of hyperphosphorylated paratarg-7, which is autosomal-dominantly inherited, has been recently identified as a risk factor in both German and Japanese carriers and may be another link to the familial inheritance pattern.[32,33]

BIOLOGY/PROGNOSTIC FACTORS

Multiple myeloma is a heterogeneous disease with varying clinical manifestations, chromosomal abnormalities, and molecular characteristics.[34] The more frequent chromosome abnormalities include hyperdiploidy, translocations involving the immunoglobulin heavy chain, monosomy of chromosome 13, gains of chromosome 1q, and deletion of 17p. Hyperdiploidy commonly involves chromosomes 3, 5, 7, 9, 11, 15, 19, or 21 and can be subdivided into four clusters which may have predictive and prognostic value.[35] Cluster 1 was characterized by high expression of the cancer testis antigen and proliferation-associated genes, a higher plasma cell labeling index (median value 3.8, $p< 0.05$) and shorter survival (median survival of 27 months) compared to the other clusters. Cluster 3, which involves the nuclear factor kappa-β and tumor necrosis factor pathways was shown to include disease that was more responsive to bortezomib (70% vs. 29% for the other clusters, $p=0.02$). Translocations of the immunoglobulin heavy chain (14q32) frequently occur with partners such as CCND1 (11q13), FGFR3 (4p16), MMSET (4p16), and MAF genes (16q23 and 20q11). These translocations are present in approximately 40% of MM patients and may contribute to the pathogenesis of multiple myeloma.[36-41] Monosomy 13 (approximately 50% of MM patients), gain of Chromosome 1q21 (approximately 33% MM patients), and deletion of Chromosome 17p (approximately 10% of MM patients) are other frequent chromosomal abnormalities and are associated with poor prognosis in patients with MM.[42-44]

Although many of the chromosomal and molecular profiling studies have been performed in the United States and Europe, there are several studies showing chromosome abnormalities in patients with MM in Asia and South America. A study by Nimura et al performed chromosome analysis on 48 patients with plasma cell disorders and found that 40.5% of patients with MM had chromosomal abnormalities.[45] Monosomy of chromosome 13 was frequently observed and was associated with resistance to chemotherapy and decreased overall survival in this cohort. In Korea, a study by Bang et al performed FISH on specimens from 128 patients with MM and found 13q deletions in 48%, trisomy 1q in 45%, immunoglobulin heavy chain gene translocations in 37%, and trisomy 11 in 26% of patients.[46] In this cohort, the stage of disease was significantly associated with 13q deletions. In Venezuela, Quintero et al found that 68% of patient samples had structural chromosomal abnormalities including hyperdiploidy in 16%, hypodiploidy in 21%, and structural abnormalities in 21% of cases.[47] In 252 patients with MM from Brazil, Ortega et al evaluated the frequency of activating mutations for the N-RAS and K-RAS gene.[48] Mutations in RAS genes were found in 21% of patients which was lower than reported in the United States and European literature where rates of up to 54% have been found. The RAS activating mutations that the investigators found included a unique site at codon 7 which has not been seen in the other cohorts.

Molecular classification of MM was performed by Zhan et al. using mRNA expression profiles from CD138 enriched plasma cells obtained from patients at the University of Arkansas for Medical Sciences.[49] The investigators found seven disease subtypes: 1) overexpression of the MMSET or FGFR3 gene; 2) upregulation of MAF genes; 3) upregulation of CCND1; 4) upregulation of CCND3; 5) hyperdiploidy; 6) low DKK1 expression; 7) high expression of genes involved in proliferation. These categories were shown to have the ability to divide MM patients into high and low risk groups for event-free and overall survival as well as risk for bony involvement. A more recent molecular analysis was performed by Broyl et al. in purified CD138 plasma cells from patients in the Dutch-Belgian/German HOVON group.[50] This study confirmed six of the clusters from the prior study as well as three other novel subgroups:
1) high expression of genes involved in the nuclear factor kappa light-chain-enhancer of activated B cells pathway;
2) overexpression of cancer testis antigens without overexpression of proliferation genes;
3) up-regulation of protein tyrosine phosphatases.

These recurring cytogenetic and molecular abnormalities have been used to predict the clinical course and guide therapy in patients with MM. The Mayo clinic developed a stratification of MM by high and standard-risk cytogenetic changes obtained from fluorescent in-situ hybridization (FISH) or conventional karyotyping (Table 2).[51] The high-risk category included deletion of 17p, t(4;14), t(14;16), t(14;20), deletion of chromosome 13 or hypodiploidy by conventional karyotyping. The standard-risk category included MM patients with hyperdiploidy, t(11;14), or t(6;14). Gene expression profiling has also been used to create high-risk categories. A 70-gene model was developed at the University of Arkansas for Medical Sciences and a 15-gene model by the Intergroupe Fancophone du Myelome, both of which found high-risk categories for decreased overall survival.[52, 53] These classifications may have therapeutic implications because data from Haessler et al. has shown that high-risk patients achieving a CR have better long-term survival than high-risk patients with less than a CR.[54]

CLINICAL PRESENTATION AND STAGING

The plasma cell disorders include MGUS, smoldering multiple myeloma, and multiple myeloma (Table 3).[55] MGUS is characterized by a monoclonal protein that is quantified at < 3.0g/dL and bone marrow plasma cell infiltration < 10% with no signs of end-organ damage related to the plasma cell disorder. Smoldering multiple myeloma (SMM) is defined as a monoclonal disorder with either a monoclonal protein > 3.0g/dL or bone marrow plasma cell infiltration ≥ 10% and no signs of end-organ damage. Multiple myeloma is diagnosed when a monoclonal protein is present with plasma cell infiltration ≥ 10% and end-organ damage related to the monoclonal protein. There are approximately 1-3% of patients with MM that may have a nonsecretory form where a heavy or light chain is not produced. Organs that are frequently involved include the bone marrow, kidney, and bone. Extensive plasma cell infiltration in the marrow can lead to cytopenias resulting in symptoms such as fatigue and dyspnea. Plasma cell dysfunction can cause hypogammaglobulinemia with an increased susceptibility to infections. Bony involvement causes lytic lesions with bone pain and hypercalcermia. The monoclonal protein secreted by the plasma cell may lead to hyperviscosity, neuropathy, renal damage, or clotting abnormalities.

Two large cohorts showed that MGUS is a common precursor lesion that develops into MM in a large percentage of patients. All 71 cases of MM enrolled in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial had evidence of MGUS in pre-diagnosis samples.[56] Another study of 30 cases of MM also evaluated pre-diagnosis samples from the U.S. Department of Defense Serum Repository and found that 27 of the cases had preceding MGUS.[57] Based on observations by Rosinol et al, there may be two different types of SMM: 1) Evolving SMM and 2) Non-evolving SMM.[58] Evolving SMM was characterized by a progressive increase in the monoclonal protein with a median time-to-progression (TTP) of 1.3 years while non-evolving SMM had a longer latency period followed by an abrupt progression and median TPP of 3.9 years.

The most frequently staging systems used for MM are the Durie-Salmon and International Staging System (ISS) (Table 4).[59,60] The Durie-Salmon staging system was based on a study of 71 patients with multiple myeloma where the myeloma cell mass was shown to correlate to the extent of bone lesions, hemoglobin, serum calcium, and monoclonal proteins in the serum and urine. Although the Durie-Salmon Staging System provides information regarding the tumor load, the subjectivity of the skeletal survey may be an important limiting factor that significantly impacts the assigned stage. The ISS was published in 2005 and represented 10,750 newly diagnosed patients with MM from 15 different countries including Canada, the United States, several European nations, and Japan. In this large cohort, the serum creatinine, serum albumin, serum beta2-microglobulin, age, and platelet count strongly predicted survival. The investigators found that combining the serum beta2-microglobulin and serum albumin level provided a straightforward and reproducible measure significantly correlating with median survival. The percentage of patients in each stage and median survival were as follows: Stage I 28% and 62 months; Stage II 33% and 44 months, and Stage III 39% and 29 months.

Table 3. **Criteria defining monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and multiple myeloma[55]**

Monoclonal Disorder	Monoclonal Protein & Bone Marrow Plasma Cell %	End-organ Damage
Monoclonal Gammopathy of Undetermined Significance (MGUS)	M-protein < 3g/dL **and** Plasma cell % < 10%	None Present
Smoldering Multiple Myeloma (SMM)	M-protein ≥ 3g/dL **and/or** Plasma cell ≥ 10%	None Present
Multiple Myeloma (MM)	Serum or Urinary M-protein present **and** Plasma cell ≥ 10%	Present and related to the monoclonal disorder **1)** Serum creatinine ≥ 2mg/dL or Creatinine clearance < 40 mL/min **2)** Serum Calcium > 11.5mg/dL **3)** Bony lesions defined as lytic lesions, osteopenia, or a pathologic fracture **4)** Anemia defined as Hemoglobin < 10g/dL or > 2g/dL below the lower limit of normal

These staging systems have been applied to ethnicities that may not have been adequately represented in the original ISS study including AA patients with MM. However, a similar staging system proposed by the Southwest Oncology Group (SWOG) in 2003 did show the prognostic value of combining serum albumin serum and serum beta2-microglobulin in 1,555 MM patients of which 19% were AA.[61] Investigators have tested the validity of the ISS to patients with MM from non-represented nations including Brazil, Chile, China, and Korea. In a large Brazilian cohort of 1,112 patients, data was available on 756 patients for staging.[62] The percentages and median overall survival by ISS stage were as follows: Stage I 20.1% and median survival not reached, Stage II 48.7% and 65.5 months, and Stage III 31.2% and 26 months, respectively.
The Durie-Salmon staging system was also applied to the Brazilian cohort, however, considerable overlap between the curves for Stage I and II was observed. Corte' et al applied both the Durie-Salmon staging and ISS to 81 patients with multiple myeloma from Chile.[63] They found that both staging systems had prognostic value, although the ISS had statistically significant differences for overall survival between all three stages (ISS Staging: Stage I 34% of patients and median overall survival 67 months, Stage II 35% of patients and median overall survival 29 months, Stage III 31% of patients and median overall survival 14 months). There have

Table 4. **Durie-Salmon and International Staging System criteria and relationship to prognosis[59, 60]**

Stage	Durie-Salmon Staging System	International Staging System	Prognosis (median overall survival)
I	Hemoglobin > 10g/dL Serum Calcium < 12mg/dL Normal skeletal survey IgG < 5g/dL or IgA < 3g/dL Bence Jones Protein < 4g/24hours	Serum albumin ≥ 3.5mg/dL Serum beta2-microglobulin < 3.5 mg/dL	62 months
II	Neither Stage I nor III	Neither Stage I nor III	44 months
III	Hemoglobin < 8.5g/dL Serum Calcium > 12mg/dL Multiple lytic lesions IgG > 7g/dL or IgA > 5/dL Bence Jones Protein > 12g/24hours	Serum albumin < 3.5mg/dL Serum beta2-microglobulin ≥ 5.5 mg/dL	29 months
A	Serum Creatinine < 2mg/dL		
B	Serum Creatinine > 2mg/dL		

been conflicting results based on data from smaller cohorts of Chinese patients not showing the prognostic value of the ISS versus Yang et al who recently found that the ISS significantly correlated to overall survival in 389 patients with MM.[64-66] In this larger cohort of Chinese patients with MM, based on the ISS 15% of patients were classified as Stage I, 29% Stage II, and 56% Stage III with corresponding median survivals of 57, 27, and 13 months. The ISS and Durie-Salmon Systems were also used to stage 85 MM patients from Korea. Although the Durie-Salmon System did not correlate with survival, the ISS did show significant differences in overall survival by stage confirming its predictive value in this cohort (Stage I: 13%, 78.6 months; Stage II: 35%, 31.8 months; Stage III: 52%, 15.1 months for percentages of patients and median overall survival, respectively).[67] Based on this data, it appears that the ISS is applicable to cohorts of patients that were not originally included in the multi-national study for providing prognostic value (Table 5).

THERAPY

The current recommendation for when to initiate therapy is when organ damage related to MM is present. Patients with MGUS should have the monoclonal protein evaluated every six months for two to three years and annually thereafter while patients with SMM should have the monoclonal protein, renal function, hemoglobin, and serum calcium evaluated every three months with annual skeletal surveys. There is a clinical trial underway addressing whether there is benefit to starting lenalidomide-dexamethasone therapy for SMM. An interim analysis of high-risk patients (defined as having bone marrow plasma cell percentage ≥ 10% and monoclonal protein ≥ 3g/dL, immunophenotyping showing ≥ 95% aberrant plasma cells, or abnormal free-light chains) showed that progression to active MM is reduced with lenalidomide treatment.[68] At a median follow up of 16 months, none of the patients in the lenalidomide-dexamethasone arm had progressed while 8 patients in the abstention arm progressed with 6 of the 8 having symptomatic bone disease. However, long-term effects including long-term toxicity and overall survival are still pending.

With advancements in therapies for MM, the overall survival of patients has improved.[69-71] Major advances have included the use of alkalyting agents, high-dose chemotherapy with autologous stem cell transplant (ASCT), and the novel agents including the immunomodulatory (IMiDs) agents, thalidomide and lenalidomide, and the proteosome inhibitor, bortezomib.

The decision for ASCT should be based on age, comorbidities, and functional status. The strongest evidence for improved response rates and prolonged survival is based on two randomized studies of patients with MM that were 65 years of age or younger. The first by Attal et al randomized 200 patients from France and Belgium to either conventional chemotherapy or high-dose therapy with ASCT.[72] Patients in the ASCT arm had higher overall response rates (81% vs. 57%, p<0.001) and five-year survival (52% vs. 12%, p=0.03) when compared to the conventional treatment arm. A second trial of 407 patients from the United Kingdom and New Zealand randomized patients to either standard therapy or intensive therapy with ASCT.[73] The rate of complete response (CR) (44% vs. 8%, p<0.001) and overall survival (54.1 months vs. 42.3 months, p=0.04) were again significantly higher in the intensive treatment arm with ASCT. Due to conflicting results on the effect of overall survival for a tandem transplant, the International Myeloma Working Group currently suggests a tandem ASCT for those patients who did not receive an optimal response (defined as VGPR or better) after the first ASCT.[74] With the advent of highly effective novel agents, several questions have arisen including upfront or delayed ASCT and the role of tandem ASCT versus either consolidation chemotherapy or maintenance therapy incorporating novel agents. Prior to novel agents, early ASCT was associated with a longer event-free survival and quality of life when compared to delaying ASCT at the time of relapse in a French cohort and so the current standard of care is to perform early ASCT.[75] The latter question is being addressed in a multi-center Blood and Bone Marrow Transplant Clinical Trials Network study where patients are being randomized to either a tandem ASCT, four cycles of consolidation therapy, or maintenance therapy. This is based on studies showing that novel agents used in consolidation therapy affect rates of CR and molecular remission while maintenance therapy incorporating a novel agent affects progression-free survival and possibly overall survival post-ASCT.[76-84]

Thalidomide was the first IMiD to show efficacy for MM in the relapsed/refractory setting.[85] In a study of 84 patients from the United States who had relapsed or refractory MM treated with thalidomide, 32% had a response. Since 1999, several studies have shown the efficacy of thalidomide in the relapsed/refractory setting including a

Table 5. **Median overall survival in months from patients with multiple myeloma in Brazil, Chile, Korea, and China based on the International Staging System (ISS)**[62, 63, 66, 67]

ISS Stage	Brazil	Chile	Korea	China
I	Not Reached	67	57	78.6
II	65.5	29	27	31.8
III	26	14	13	15.8

systematic review showing response rates of approximately 30% as monotherapy and 46% for thalidomide with dexamethasone.[86] Thalidomide has also been shown to have efficacy in the front-line setting. In an Eastern Cooperative Oncology Group (ECOG) study of 207 newly diagnosed MM patients randomized to either thalidomide/dexamethasone versus dexamethasone, the thalidomide/dexamethasone arm showed significantly higher response rates (63% vs. 41%, p=0.0017) but at a cost of higher toxicity including deep vein thrombus and neuropathy.[87] Another study comparing induction with thalidomide/dexamethasone to vincristine/adriamycin/dexamethasone (VAD) followed by high-dose chemotherapy and ASCT in 203 newly diagnosed MM patients found higher rates of a very good partial response (VGPR) or higher in 24.7% of patients treated with thalidomide/dexamethasone versus 7.3% in the VAD arm.[88]

Lenalidomide was developed as an analog to thalidomide with the hopes of reducing therapy-related toxicity. Based on very encouraging results from a Phase I trial showing 71% of patients in the relapsed setting having clinical benefit, lenalidomide was combined with dexamethasone in the front-line setting.[89] In a Phase II study from the Mayo Clinic of newly diagnosed patients with MM treated with lenalidomide and dexamethasone, an objective response rate of 91% was observed.[90] In a phase III ECOG study of 445 newly diagnosed MM patients that were randomized to lenalidomide with either high-dose or low-dose dexamethasone regimens, although higher response rates were seen in the lenalidomide/high-dose dexamethasone arm (82% vs. 70%, respectively), lower rates of Grade 3 or higher toxicity (30% vs. 50%, respectively) and higher rates of overall survival were seen in the lenalidomide/low-dose dexamethasone arm (87% vs. 70% at 2 years follow up, respectively).[91]

Bortezomib is a proteosome inhibitor whose first Phase II study was in 202 patients from the United States, including 10% African Americans, with relapsed/refractory MM and showed a 35% response rate in heavily pre-treated patients.[92] In the upfront setting, a phase III IFM study of 482 patients with newly diagnosed MM were randomized to either bortezomib/dexamethasone or VAD followed by a second randomization for two more cycles of chemotherapy with dexamethasone, cyclophosphamide, etoposide, and cisplatin and then ASCT versus going directly to ASCT after induction therapy.[93] Induction with bortezomib showed higher rates of CR or near CR (14.8% vs. 6.4%, respectively), VGPR or higher (37.7% vs. 15.1%, respectively), and overall response rate (78.5% vs. 62.8%) with a trend towards prolonged progression-free survival (36 vs. 29.7 months, p=0.064).

Combinations of two novel agents have shown further improvements in high-quality responses and progression-free survival. Phase III trials from Italy, Spain, and France using a regimen of bortezomib, thalidomide, and dexamethasone (VTD) have shown overall response rates of 85-93% with responses of VGPR or higher of 51-60%.[94-96] A Phase I/II study evaluating the efficacy of lenalidomide, bortezomib, and dexamethasone in newly diagnosed MM found a 100% overall response rate in the Phase II population with 74% achieving a VGPR or higher and a favorable toxicity profile.[97]

In those patients that are not eligible for ASCT, particularly the elderly, novel agents have been combined with melphalan and shown to have significant impacts on response rates and survival. Two large Phase III trials have evaluated the efficacy of thalidomide with melphalan and prednisone. The first compared melphalan, thalidomide, prednisone (MPT) to melphalan and prednisone (MP) in 255 newly diagnosed MM patients older than 60 years from Italy. Higher overall response rates and CR/nearCR were seen in the MPT arm (76% vs. 47.6% and 27.9% vs. 7.2%, respectively).[98] The other Phase III trial conducted by the IFM evaluated MPT to MP or reduced-intensity ASCT in 447 untreated MM patients between the ages of 65 and 75 years old.[99] Although response rates were similar between the MPT arm and the reduced-intensity ASCT arm, significantly higher overall survival was seen in the MPT arm (51.6 vs. 38.3 months, respectively; p=0.027). A large Phase III trial addressed the efficacy of the addition of bortezomib to melphalan and prednisone in 682 transplant ineligible patients from 22 countries including from North America, Europe, Asia, and South America.[100] The patients treated with bortezomib, melphalan, and prednisone had significantly higher PR or better responses (71% vs. 35%, p<0.001), CR (30% vs. 4%, p<0.001), and time to progression (24 months vs. 16.6 months, p<0.001). Data combining lenalidomide with melphalan and prednisone is based on a Phase I/II study from Italy of newly diagnosed MM patients 65 years or older where a 81% overall response rate and 23.8% CR rate were observed.[101]

The therapeutic impact of high-dose chemotherapy with ASCT appears to have similar benefit in AA as non-AA based on several observational studies.[102-105] Two large population studies have also evaluated the outcomes of AA patients with MM in the United States to non-AA. The first by Rohatgi et al found comparable survival benefits to chemotherapy in AA (hazard ratio=0.72, 95% CI 0.61-0.86) as Caucasians (hazard ratio=0.63, 95% CI 0.58-0.67), although AA were 23% less likely to receive chemotherapy.[106] The second population study compared survival rates between AA and non-AA through different eras of therapy.[107] The overall relative survival rate and disease-specific survival rates were higher in AA than Caucasians with MM. However, the Caucasian cohort had significant improvements in their 5-year survival rates through the different eras (26.3% in 1973-1993 era, 30.8% in 1994-1998 era, 35.0% in 1999-2005 era) whereas the AA cohort did not show a significant

improvement from the 1994-1998 era to the 1999-2005 era (31.0% in 1973-1993 era, 33.0% in 1994-1998 era, 34.1% in 1999-2005 era). From the data, it appears that although AA may have similar responses to therapeutic agents for MM, access to care may lead to outcome disparities.

The efficacy of high-dose chemotherapy followed by ASCT has also been evaluated in other nations not typically represented in the previously mentioned trials. In Japan, a study comparing 90 patients treated with ASCT versus 60 historical controls showed significant improvements in median survival (76 vs. 28 months, $p<0.0001$).[108] A retrospective study of 86 patients with MM from China compared patients receiving ASCT to those patients that achieved a CR or PR without ASCT.[109] In the patients that were treated with ASCT, 43% achieved CR and a longer duration of response of 33 months was observed in comparison to 17 and 18 months in those patients in CR and PR without undergoing ASCT, respectively. The experience in India has also shown substantial response and survival rates with ASCT in MM. A report of 143 patients treated from 1990 to 2009 showed a 83.3% response rate (CR 40.6%, VGPR 25.9%, PR 16.8%) with a median event-free survival of 30 months and overall survival of 79 months.[110] Similar survival rates were observed in a study of 26 MM patients from Mexico treated with intravenous melphalan followed by ASCT (median disease-free survival 38 months, median overall survival 86 months).[111]

Although one of the larger Phase III trials assessing the efficacy of a novel agent (bortezomib with melphalan and prednisone by San Miguel et al) included patients from South America and Asia, most of the previously mentioned studies showing efficacy of the novel agents were limited to MM patients from the United States and Europe. There have been several Phase II studies from Japan showing the clinical utility of thalidomide, bortezomib, and lenalidomide in the relapsed/refractory setting. One such study of 66 Japanese MM patients treated with low-dose thalidomide and dexamethasone showed overall response rates of 63.6% with progression-free and overall survivals of 6.2 and 25.4 months.[112] In 25 patients with relapsed/refractory MM from Japan, lenalidomide plus dexamethasone was shown to be highly effective (PR or higher response seen in 100% of the patients) with two-thirds having grade 3 or 4 neutropenia.[113] Bortezomib with dexamethasone has also shown efficacy in Japanese MM patients with relapsed/refractory disease based on a study of 88 patients showing an overall response rate of 66.9%, median overall survival of 16.8 months, and progression-free survival of 6.8 months.[114] Of note, the toxicity profile in Japanese patients treated with thalidomide and bortezomib have been different from European and United States studies. Thalidomide was shown to cause higher incidences of leukopenia (41%) and grade 3 leukopenia (11%) and lower rates of peripheral neuropathy and deep vein thrombosis in the Japanese MM patients.[112] Pharmacokinetic studies suggest that there may be lower rates of clearance and volume of distribution, and higher area under the plasma concentration-time curve in Japanese patients with MM than Caucasian patients and may explain the differences in the toxicity profile.[115] Life-threatening lung injury has been associated with bortezomib and possibly thalidomide therapy in Japanese patients with MM.[116-118] In a cohort of 13 Japanese MM patients being treated with bortezomib at a single center, four developed severe pulmonary complications with two deaths unrelated to progression of disease. A questionnaire-based report was soon published thereafter showing that seven of 46 patients (15.2%) developed pulmonary complications either definitely or probably related to bortezomib. Of the seven patients, three died of respiratory failure.

Novel agents have also proven effective in Korea for treating MM patients either as single agents, combined with other chemotherapy agents, or with two novel agents with similar toxicity profiles to the western literature. A multicenter, retrospective study included 95 patients who received bortezomib only (n=38 patients), bortezomib plus dexamethasone (n=34 patients), and bortezomib plus thalidomide-containing regimen (n=23 patients) and showed an overall response rate of 65% (CR/nearCR 33%, PR 32%).[119] The use of novel agents for induction with two cycles of VAD followed by 2 cycles of bortezomib/thalidomide/dexamethasone followed by ASCT in newly diagnosed Korean MM patients showed a response rate of 97% with CR/nCR of 27% and median time to progression of 20.3 months.[120] For those deemed non-transplant eligible, the combination of bortezomib/thalidomide/dexamethasone induction followed by consolidation with melphalan/prednisolone/thalidomide was evaluated in 35 Korean patients with MM.[121] Early responses were observed in 97% of patients with 30% having VGPR or higher responses. These response rates were observed in both high and standard-risk patients, based on cytogenetic abnormalities, with

ANSWER - (To Medical Image - page 19)

Bone marrow necrosis

Bone marrow biopsy shows fibrinoid necrosis, ghost cells with acute inflammation and macrophages. Diagnosis of myelodysplastic syndrome (refractory anemia with excess blasts) was made. Bone marrow necrosis (BMN) is a rare clinicopathologic entity with grave prognosis. It was first reported by Wade and Stevenson in 1941.[1] It is distinct from avascular necrosis of bone and bone marrow aplasia; and is characterized by necrosis of myeloid tissue and medullary stroma with loss of fat spaces.

Pain, fever and fatigue are common symptoms. Lactate dehydrogenase and alkaline phosphatase are found to be elevated in approximately 50% of the patients. In a study by Janssens AM,[2] underlying malignancy was found in ninety-one percent of the patients. Hematologic malignancies are the most common causes of BMN. Other etiologies include solid tumors, infection, medications and sickle cell disease. Given its common association, extensive search for malignancy is indicated in patients presenting with unexplained bone marrow necrosis.

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two-year overall survival rates of 60% and 85%, respectively. A regimen containing both thalidomide and bortezomib was found to be effective in the relapsed/refractory setting for Korean patients as well.[122] The overall response rate was 88% (CR 46%, VGPR 9%, PR 33%) with a median progression-free survival of 14.6 months.

Novel agents appear to improve prognosis in patients with MM from China as well. Li et al reported overall response rates of 63.6% (CR 6.4%, PR 57.3%) in 110 Chinese patients with MM treated with thalidomide in the salvage setting.[123] Based on survival data comparing median overall survival of 389 Chinese MM patients, median overall survival improved from 15.3 months in the 1996-2001 era to 28.2 months in the 2002-2007 era (p=0.002) when more patients had received thalidomide therapy despite having an older age at diagnosis in the second time era.66 The combination of thalidomide/bortezomib/dexamethasone in newly diagnosed MM was also shown to be effective in 20 Chinese patients with a 95% response rate (CR 15%, PR 80%).[124] A larger study in China included 47 newly diagnosed and 63 relapsed/refractory MM patients and assessed response to bortezomib-based regimens which included combinations with melphalan, doxorubicin, or thalidomide.[125] The overall response rates were 83% and 71.4% with CR+VGPR rates of 73.7% and 40% in newly diagnosed and relapsed/refractory patients, respectively.

In Mexico, a retrospective comparison of induction with VAD to thalidomide and dexamethasone was performed in 88 patients with MM.[126] The thalidomide/dexamethasone group had a response rate of 84.3% (CR 18.8%, nCR/VGPR 18.8%, PR 46.5%) which was significantly higher than the response rate in the VAD group of 55% (CR 16%, nCR/VGPR 5%, PR 34%) (p=0.0005). In India, 99 patients were treated with thalidomide including 36 being treated in the frontline setting and 63 for relapsed cases.[127] Similar response rates and toxicities were observed in this cohort in comparison to the western literature with objective responses in 88.9% of frontline treated patients and 52.4% in relapsed cases. A study from Turkey randomized 122 patients that were transplant ineligible to either MP or MPT. They found higher rates of PR or better in the MPT arm in comparison to the MP arm (57.9% vs. 37.5%, p=0.03,) with a nonsignificant improvement in disease-free survival (21 vs. 14 months, p=0.34).[128] Higher rates of grade 3 or 4 infections were seen in the MPT arm, although none were associated with febrile neutropenia and more deaths within the first three months of therapy were seen in the MP arm.

CONCLUSION

Multiple myeloma is a heterogeneous disease with incidence rates that vary by ethnicity. Some risk factors such as MGUS, age, and sex are consistent across ethnicities although etiologies for differences in epidemiology are not fully understood. Prognostic factors such as cytogenetic abnormalities and ISS staging do appear similar, although some variations are noted. Improvements in response rates and survival have been seen with ASCT and novel agents. The efficacy of these therapies has also been observed in different ethnicities from United States, Europe, Asia, and South America. However, it is important that toxicities be carefully understood in different races due to potential differences in metabolism. Overall, since several reports have shown parallel improvements in therapeutic responses across the continents, it is of critical importance that future studies of long term outcome of MM patients will be monitoring an adequate and equal access to care in each country.

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