HHS Public Access

Author manuscript

Semin Oncol. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Semin Oncol. 2016 December ; 43(6): 676–681. doi:10.1053/j.seminoncol.2016.11.004.

Multiple myeloma epidemiology and survival, a unique malignancy

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Abstract

Multiple myeloma (MM), although a rare disease, is the second most common hematologic malignancy. It is found in the spectrum of plasma cell dyscrasias which begins with monoclonal gammopathy of unknown significance to overt plasma cell leukemia and extramedullary myeloma. MM is associated with significant morbidity due to its end-organ destruction. It is a disease of the older population and its incidence in the African American population is twice that of the European American population. Improvements in the treatment of MM in the past couple of decades, beginning with the use of autologous stem cell transplantation followed by availability of novel treatments such as immunomodulatory drugs and proteasome inhibitors has transformed the natural history of the disease leading to longer survival times. Advancements in the diagnosis, monitoring, and treatment of MM are of the utmost importance as the general population lives longer due to other improvements in health care. The recent introduction of novel therapies has been paralleled by advancements in the monitoring of MM, namely, by the availability exquisitely sensitive techniques in detecting minimal residual disease. As drug development and technology continues to improve, it will be important to design rationale clinical trials enrolling patient populations which represent the overall population including racial minorities and the elderly so trial results can be appropriately extrapolated. This manuscript reviews the changing epidemiology, the improvements in survival, and the health disparity observed in important subgroups of MM.

Keywords

multiple myeloma; smoldering myeloma; MGUS; epidemiology; health disparity

Introduction

Significant advances have been made in understanding multiple myeloma (MM) and its precursor diseases. These advances include the gain in knowledge in the underlying

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pathophysiology, Food and Drug Administration (FDA) approvals of novel therapies with meaningful efficacy, tempo of drug development, and the science in underlying disparities in patients with MM. This manuscript aims to review the diagnosis, natural history, and epidemiology of MM and give further insight and steps forward into the disparities observed in MM.

MM is a neoplasm of clonal plasma cells which originate from the post-germinal lymphoid B-cell lineage and develop after lineage commitment in the bone marrow of progenitor cells.[1] Plasma cell dyscrasias encompass a spectrum of disease which include asymptomatic premalignant proliferation of plasma cells (monoclonal gammopathy of unknown significance [MGUS]) and asymptomatic MM (smoldering MM (SMM)) to malignant disease (MM and plasma cell leukemia) with end-organ damage and associated significant patient morbidity.[2,3] Investigators have determined that almost all cases of MM evolve from the MGUS precursor stage.[4,5] However, most cases of MGUS do not progress to a malignant neoplasm and other than overt MM some develop into Waldenstrom's macroglobulinemia, primary AL amyloidosis, or a lymphoproliferative disorder.[6,7] The risk of progression to MM or a related disorder is estimated to be 1% per year. MGUS is one of the most common pre-malignancies with a 3% prevalence in the white population 50 years of age or older and is approximately double in the African American population.[4,8,9]

SMM was first described in 1980, when six patients meeting the laboratory criteria of MM never developed end-organ damage.[10] Similar to MGUS, not all SMM cases evolve to symptomatic MM with end-organ damage, however, all cases of MM evolve from SMM. Numerous risk stratification techniques have been devised, notably the Programa para el Tratamiento de Hemopatias Malignas (PETHEMA) and Mayo criteria, to determine patients who are most likely to progress to MM.[1,11] Nevertheless, in all patients with SMM, the overall risk of progression based on a small cohort study was found to be 10% per year for the first 5 years, 3% per year in the next 5 years, and 1% per year afterward; the cumulative probability of progression was 73% after 15 years.[12] Due to the heterogeneous natural history and outcomes of patients with SMM and lack of efficacy with universal treatment in earlier studies, it is not treated outside of clinical trials. However, with the advent of novel therapies and improved risk stratification, this might change in the near future. A recent randomized study, albeit with many caveats, did suggest benefit in treating patients with high risk SMM with lenalidomide and dexamethasone.[13,14]

The International Myeloma Working Group (IMWG) by consensus defined MGUS, SMM, and MM in 2003 and subsequently slightly refined the criteria in 2010, and then significantly refined the diagnostic criteria in 2014.[15,16] In brief, MGUS was defined fined as the presence of serum M-protein < 3 g/dL and < 10% monoclonal plasma cells in the bone marrow (BM). SMM was defined as either the presence of serum M-protein ≥ 3 g/dL or ≥ 10% monoclonal plasma cells in the BM. MM was defined as the presence of end-organ (classic "CRAB" criteria) damage in parallel with the presence of an M-spike and/or monoclonal plasma cells. In 2014, the IMWG changed the diagnostic criteria for SMM/MM. Specifically, patients with "ultra-high risk" SMM defined on the basis of prognostic variables identifying patients with a ≥ 80% risk of progression within 2 years were re-categorized as having "low-risk" MM and therefore ought to be treated despite the lack of

traditional “CRAB” criteria. The prognostic variables (based on evidence from two or more trials) meeting this criteria were ≥ 60% BM plasma cell burden, an involved/uninvolved light chain ration of ≥ 100, and the appearance of > 1 lytic lesion on MRI of the spine.[17]

Multiple Myeloma Epidemiology: Incidence, Survival, and Racial Differences

MM accounts for 1% of all cancers and is the 2nd most common hematologic malignancy after lymphoma with an estimated 24,2802 to 30,330 new cases and 12,650 deaths to occur for 2016.[2,18,19] The estimated world-wide 5-year prevalence is approximately 230,000 patients.[20] In the Western world, the age-standardized incidence has been reported to be approximately 5 cases per 100,000.[21,22] The median age of patients at diagnosis is approximately 66–70 years with 37% of patients being younger than 65 years of age.[2,23] MM is extremely rare in those less than 30 years of age with a reported frequency of 0.02% to 0.3% and appears to occur slightly more frequently in men.[24,25] In general, MM is not considered to be a genetic disease, however familial cases, albeit rare, do exist.[26] Interestingly, it was observed that relatives of patients with MGUS compared to normal controls had a higher relative risk of developing MGUS (2.8 fold), MM (2.9 fold), Waldenström macroglobulinemia (4.0 fold), and chronic lymphocytic leukemia (2.0).

Most importantly, in the past decade survival rates have improved significantly for the general population most likely due to the availability of effective therapy beginning with autologous stem cell transplant (ASCT).[27,28] It has been reported that median survival in patients with relapsed MM prior to 2000 was 12 months compared to 24 months for after 2000.[29] Modern therapies, notably, the immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), have further led patients with MM to survive longer as has been observed with incremental improvements in 5- and 10- year survival rates. In another study, 5-year relative survival was found to increase from 34% in 1989–1992 to 56% in 2001–2005 periods of diagnosis.[30] Based on the surveillance, epidemiology, and end results (SEER) data, Siegal et al. reported that 5-year relative survival rates in MM improved to 49% for the 2005–2011 year period compared to 25% for 1975–1977 and 27% for 1987–1989.[19] Interestingly, the 2005–2011 period coincides with the first PI and IMiD approvals (bortezomib: 2003; thalidomide/lenalidomide 2006). Indeed in a 2008 Mayo report, patients who received one of the aforementioned PI or IMiDs had longer survival from relapse (31 vs 15 months) and patients who had been diagnosed in the last decade had an almost doubling in median survival time.[29]

One area of uncertainty and apparent controversy is whether the older MM patient population have also benefited by the recent improvements in survival. For example, in a Swedish cohort diagnosed between 1973–2003, patients older than 60 years of age did not have improved 5-year survival rates.[27] This was also observed in another Swedish study where between the years 1950–2005, improvement in incremental 10-year survival rates were only observed for patients ≤ 65 years of age.[28] A report from the Netherlands of MM diagnoses between 1989–2005 found that patients > 65 years old who were diagnosed between 1989–1992 or 2001–2005, had the exact same 5-year survival rate of 24%.[30] One

possible explanation for the lack of benefit in older patients was that high dose ASCT therapy could only benefit the younger age group due to ineligibility and toxicity. However, in another analysis, some modest improvement in survival was observed in patients age 60–79 compared to younger patients but no improvement in those ≥ 80 years of age.[31] Interestingly, in a more recent analysis, it was reported that patients ≥ 65 years of age who were diagnosed between 2006–2010 compared to 2001–2005 had improved median survival times not observed in the younger group. Furthermore, another report found that for the periods of diagnosis between 2000–2009, patients ≤ 65 and 66–79 years of age but not those ≥ 80 had improved 10-year survival rates compared to earlier time periods.[32] Similar findings were observed by an independent group who performed sensitivity analyses on the SEER data sets.[33] These more recent findings of improved benefit for patients aged 60–80 after approximately 2005 is consistent with the wider availability of novel and more potent drugs for older ASCT non-eligible patients.

MM has one of the most striking, interesting, and thought provoking differences between races in both incidence and outcome.[34] Compared to European Americans (EA), MGUS and MM have been observed to occur twice as frequently in African Americans (AAs), with similar transformation rates from MGUS to MM in both races. In addition, older published descriptive studies have suggested same or worse survival outcomes in AAs. For example, a prior single-center study found poorer survival among 52 patients with MM at a predominantly AA hospital compared to 92 patients at a predominantly EA hospital.[34] Similarly, a single-institution review of records of 292 patients with MM found that neither race nor socioeconomic status independently were associated with overall survival.[34] Importantly, retrospective data from the South West Oncology Group (SWOG) showed comparable outcomes among AAs and EAs before the advent of ASCT while another small study of ASCT in an equal access health system observed no difference in survival by race. In order to further understand these differences between AA and EAs in a more systematic and generalized fashion, Landgren and colleagues evaluated the incidence and outcome using the original SEER 9 registries to conduct a large scale population-based study.[35] The cohort included 5,798 AA and 28,939 EA patients who were diagnosed between 1973–2005 and followed through 2006. The authors confirmed that the incidence of MM in AAs was twice that in EAs overall and thrice in those younger than 50 years of age. AAs also had a younger age of onset. Furthermore, as expected, 5-year survival rates improved with the advent of new therapies in EAs however, differences in the improvement of survival rates in AAs were marginal and not significant.

Although the etiology of MM remains elusive, clinical features, observed racial disparity patterns of incidence, reported familial clustering, and younger incidence in AAs suggest a role for susceptibility genes. The racial differences described cannot solely be ascribed to socioeconomic and access-to-care differences and that, at least in part, is likely to be due to deeper underlying genetic and biologic differences. In order to further understand this, Baker et al. attempted to associate specific genomic alterations to the racial clinical differences observed.[36] The authors used three platforms to evaluate different prognostic markers: fluorescence in situ hybridization (FISH), array-based comparative genomic hybridization (aCGH), and gene expression profiling (GEP). The only significant difference they observed

was a lower frequency of IgH translocations. However, the study was confounded by a small number of AAs analyzed (11 cases for FISH).

Recent advances and steps forward in the treatment of multiple myeloma

We have entered a new era in the treatment of MM and potentially smoldering MM. Moving forward, it will be important that trial designs and eligibility criteria reflect the overall population and that results may be extrapolated to the general community. More recently, the relatively low frequency of US patients enrolled on clinical trials has been a matter of discussion. Many agree, that in general, more patients in the US should be enrolled on clinical trials from the estimated 3–5% and that eligibility criteria of trials should be modified to include pertinent subgroups.[37] Regarding MM, a recent report analyzing 128 MM manuscripts and comparing the findings to unselected patients from SEER-18 found that patients enrolled on trials were younger in age and had less advanced disease stage. Importantly, only 40% of trials reported the ethnic/racial composition of patients enrolled on the trials concluding that the observed/expected minority accrual rate was 0.52.[38] In conclusion, as the MM treatment arena becomes ever more exciting with the introduction of novel therapeutics, special attention will have to focus on clinical trial eligibility criteria and inclusion of patients appropriately representative of the general population.

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