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Multiple Myeloma: A Clinical Overview

By Kenneth C. Anderson, MD

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Abstract / Synopsis:
Multiple myeloma (MM) is the second most common hematologic malignancy in the United States, affecting slightly more men than women and twice as many African Americans as Caucasians. Older age is the primary risk factor for MM, but obesity also increases risk. MM is incurable, but treatment advances in the past decade have more than doubled the duration of survival. MM is a progressive plasma cell tumor in which an initially stable clone becomes malignant via a multistep process. Causative factors implicated in this process include radiation, environmental toxins, chronic antigen stimulation, and genetics. The malignant plasma cells interact with other hematopoietic and stromal cells within the bone marrow microenvironment to disrupt homeostasis among cells and within the extracellular matrix. These tumor-host interactions lead to MM cell proliferation and migration, angiogenesis, osteolysis, immunodeficiency, and anemia. As a result, patients often present with osteolytic bone lesions, recurrent infections, renal insufficiency, and fatigue. The Durie-Salmon and International Staging Systems are used to stage MM, with the latter providing prognostic information based on readily available laboratory data. However, a number of cytogenetic markers are emerging as prognostic indicators, introducing the possibility of more refined disease staging systems and tailored treatment strategies based on genetic profiles.

Introduction

Multiple myeloma (MM) is a malignant, progressive plasma cell tumor characterized by overproduction of monoclonal immunoglobulins, osteolytic bone lesions, renal disease, and immunodeficiency.[1] Before the 1980s, patients with MM experienced a slow, progressive decline in quality of life until death approximately 2 years after diagnosis,[2] but the advent of high-dose alkylating agents increased the probability of remission and prolonged overall and event-free survival. During the past decade, important advances have been made in understanding the cellular and molecular mechanisms of MM, leading to the development of even more effective treatment strategies,[3,4] including stem cell transplantation, the immunomodulators thalidomide and lenalidomide, and the first-generation proteasome inhibitor bortezomib.

Currently, MM is an active field of research for novel pharmacotherapies, with a number of agents in phase II or III of clinical development. This supplement describes several therapeutic advances in the context of the underlying molecular mechanisms. The objective of this article is to put these advances into the current clinical context by providing an overview of the epidemiology, etiology, and clinical features of MM, along with the prognosis for patients with this disease.

Incidence and Mortality

According to estimates from the American Cancer Society, 20,180 new cases of MM were diagnosed in the United States and an estimated 10,650 Americans died of MM in 2010.[5] MM is the second most common hematologic malignancy after non-Hodgkin lymphoma and represented nearly 15% of new hematologic malignancies diagnosed in 2010.[5] Globally, the incidence of MM ranges from around 1 per 100,000 in China to around 4 per 100,000 in most developing countries.[1]

Although MM is currently an incurable disease, treatment advances during the past decade have translated into a decrease in the mortality rate.[6] Before the 1980s, patients usually died within 2 years of receiving a diagnosis of MM. In contrast, since the year 2000 median overall survival with treatment has ranged from 4.4 to 7.1 years.[2]

Demographics

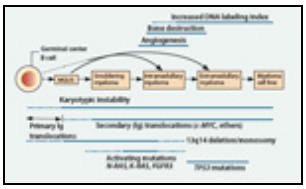
The incidence of MM is slightly higher in men than in women, and about twice as high in African Americans as in Caucasians.[1,7] Asians appear to have a lower risk of developing MM than Caucasians or persons of African descent.[8] Persons of African descent are also more likely than Caucasians to develop the MM precursor, monoclonal gammopathy of undetermined significance (MGUS).[8-10] Actually, the difference in the incidence of MM between Caucasians and African Americans appears to be the result of a higher rate of MGUS among African Americans, rather than a higher rate of conversion from MGUS to MM.[9] The racial discrepancy in MGUS or MM incidence may be partially related to socioeconomic factors,[11] although no association has been proved between the risk of MM and the socioeconomic factors of family income, education level, occupation, dwelling size, or crowding in the home,[12] or between MGUS and education level or household income.[10] In clinical trials, the age-standardized rate of death is similar across all ethnicities for patients with MM[13]; similarly, the current decline in MM mortality is seen in all ethnic groups, although it has affected Native Americans the least.[6]

MM is generally a disease of older persons.[7] The median age at diagnosis is between 61 and 68 years,[1,2,4,14] with approximately 2% of patients < 40 years.[1,14]

There is growing evidence of a significant association between being overweight or obese and the development of MM[15,16] and MGUS.[10] Overweight and obesity are also predictors of MM-associated mortality.[15] The relationship between body mass index and MM incidence is similar across sexes and ethnicities in both the United States and Europe.[15] The mechanism for this relationship is not clear, but it may involve the proinflammatory cytokines interleukin-6 or insulin-like growth factor, which may be elevated in obesity[17,18] and which mediate proliferation of myeloma cells.[18,19] There have been some indications of a familial predisposition to the development of MM, and studies are ongoing to evaluate families in which there are many individuals with myeloma.[20]

Etiology

FIGURE 1



The Pathogenic Progression of Multiple Myeloma

MM is characterized by the pernicious transformation of a plasma cell precursor into a plasma cell myeloma, and it is actually the final malignant phase of a disease process that begins with the relatively benign MGUS (Figure 1).[7] In the premalignant phase of MGUS, patients may be asymptomatic and only have elevated levels of idiotypic monoclonal (M) immunoglobulin (Ig); this phase can remain stable for many years.[7] “Smoldering” myeloma describes the transition phase between MGUS and frank MM, when patients have an intramedullary tumor cell content of >10% but no osteolytic lesions or other complications of MM.[2,7,21] Each year, about 1% of patients with MGUS progress to symptomatic MM or another form of plasma cell neoplasia.[22] The diagnosis of MM at any of these stages can be difficult; therefore, the distinctions between the phases and subtypes of myeloma have been defined by the International Myeloma Working Group (Table 1).[21]

TABLE 1

International Myeloma Working Group Criteria for Monoclonal Gammopathies and MM[21]

Progression to MM probably reflects a combination of genetic changes in the malignant plasma cell, alterations in the bone marrow microenvironment (supporting tumor growth), and failure of the immune system to control the disease.[7] The induction of MM is probably a multistep process involving formation of the initial plasma cell clone and then conversion of the stable clone into a progressive malignant tumor. Factors implicated in these processes include radiation exposure, environmental exposure, chronic antigen stimulation, and genetics.[7]

Radiation exposure

Data on the potential impact of ionizing radiation exposure on the development of MM are inconsistent.[7] The risk of developing MM,[23] but not MGUS,[24] was increased in Hiroshima/Nagasaki atomic bomb survivors—but only 20 years after radiation exposure—and the risk was dose-dependent.[23] Although the overall risk of MGUS was not increased, atomic bomb survivors tended to develop MGUS earlier than age-matched controls and showed more rapid conversion from MGUS to MM, although these findings were not statistically significant.[25] Personnel from the United Kingdom who were present at atmospheric nuclear tests and who were exposed to high-dose, short-duration radiation did not show an increase in MM incidence.[26] However, these data have been criticized for omitting some MM cases from the cohort and thereby underestimating the true MM incidence.[27] On the other hand, long-duration exposure to lower doses of radiation may be associated with a slight increase in the incidence of MM, such as that seen in individuals working in the nuclear industry.[28,29] In these individuals, older age at the time of radiation exposure, rather than lifetime cumulative radiation dose, appeared to be the more significant risk factor for MM development.[28] Radiotherapy treatments for pelvic cancers, however, do not increase the risk of MM development.[30]

Environmental exposure

An increased incidence of MM has been demonstrated in particular occupations, including farming, painting, metalworking, rubber manufacturing, woodworking, leather and textile processing, and petroleum production, although these relationships have not been consistently demonstrated across different studies.[7] Farming and agriculture have the strongest relationship to MM development[7,31]; these relationships may reflect exposure to pesticides or zoonotic infectious agents.[31]

Chronic antigen stimulation

It is possible that chronic antigen stimulation, with its associated lymphocyte activation, also plays a role in MM development.[7] A number of studies have shown a higher than expected incidence of MM among patients with rheumatoid arthritis (RA).[32-34] However, factors other than chronic antigen stimulation may play a role, such as a shared predisposition for the development of RA and MM (evidenced by simultaneous development of MGUS and RA in some patient series[35] and by a high rate of RA among

first-degree relatives of patients with MM[36]). Another factor may be the effects of medications, such as corticosteroids, which are associated with an increased risk of MM, at least in women.[37]

Certain viral infections have also been implicated, albeit with variable findings and quality of supporting data. These include hepatitis C virus,[38] hepatitis B virus,[39] and human immunodeficiency virus.[40,41]

Genetics

The familial and racial patterns of MM suggest genetic links.[7] Almost 50% of all patients with MM have a first-degree relative who has had cancer,[14] and the risk for both MM and MGUS is twice as high in persons with a first-degree relative who has had cancer.[42,43]