Introduction

Multiple myeloma [MM] is a debilitating malignancy that is a part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia. First described in 1848, multiple myeloma is a disease characterized by a proliferation of malignant plasma cells and a subsequent overabundance of monoclonal paraprotein. An intriguing feature of this disease is that the antibody-forming cells (i.e., plasma cells) are malignant and, therefore, may cause unusual manifestations. **(Barlogie 2006)** Plasma cells are a subset of B cells, which are the producers of antibodies. Antibody molecules are composed of 2 polypeptide chains: a light chain and a heavy chain. Cleavage results in the production of Fab and Fc fragments; the Fab fragment is termed the Bence-Jones protein and is found in the urine of patients with myeloma.An individual plasma cell can produce antibody molecules of only a single immunoglobulin to combine with a single antigen. As such, a plasma cell is termed monoclonal. Most infections produce a polyclonal response because multiple antigens are present on a single bacillus or virus and activate multiple plasma cells. If malignant transformation occurs in a single plasma cell, its clones produce only a single type of immunoglobulin. **(Bergsagel, 1995)**

Plasma cell dyscrasias can be divided into premalignant and malignant conditions. Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition, (which may progress to MM bye a rate of 1% per year) whereas asymptomatic MM and active MM are malignant. **(International Myeloma Working Group, 2003)** Asymptomatic MM is differentiated from active myeloma by end-organ compromise designated by the acronym "CRAB" (hypercalcemia, renal insufficiency, anemia, or bone lesions). **(Hanamura, 2006)** MGUS is defined by a monoclonal

immunoglobulin concentration in serum of 3 g/dL, the absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency, and a bone marrow with 10% plasma cells. Recently, it has been established that MGUS patients can be stratified to high or low risk patients.Patients with low-risk MGUS should be followed yearly, and high-risk MGUS patients should be followed every 3 to 6 months to evaluate for progression to myeloma. **(Fonseca, 2002)**

The cause of multiple myeloma is unknown. One theory is chronic antigenic stimulation of a plasma cell, which results in transformation and the development of myeloma. However, once a plasma cell is transformed, it is known to produce innumerable clones, which spread hematogenously to other myelogenous areas. Once there, these neoplastic cells form sheets that replace the normal bone marrow. In addition, the myeloma cells produce osteoclast-stimulating factor, a cytokine that results in bone destruction. The plasma cell activating factor interleukin-6 (IL-6) is found within bone marrow, resulting in plasma cell proliferation. The osteoblastic response in myeloma tends to be suppressed, resulting in the severe demineralization and bone destruction that are characteristic of the disease. Secondary hypercalcemia is present. **(Fonseca, 2002)** Multiple myeloma can cause a wide variety of problems. The characteristic findings in MM are lytic bone disease, renal insufficiency, anemia, hypercalcemia, and immunodeficiency. The most common presenting symptoms are fatigue, bone pain, and recurrent infections. **(Kyle, 2003)** Any of these findings should alert the clinician to the possibility of MM and warrant further clinical investigation. In newly diagnosed patients, skeletal abnormalities are present on conventional radiography in approximately 60% to 80% of patients, anemia is present in 70% of patients, hypercalcemia in 15%, and elevated serum creatinine in 20%. However, approximately 25% of patients present without symptoms and are identified incidentally by laboratory results, such as an elevated total protein, encountered during

routine testing or in evaluation of other health problems. **(Greipp, 2005)**

Multiple myeloma (MM) accounts for 1% of all malignancies: 10% of all hematological malignancies in Caucasians and 20% in African Americans. It is the second most common hematologic malignancy in the United States. The overall incidence rate in the United States is 4.4/100,000/year with a male: female ratio of 1.4:1. The reason for the higher incidence in men and African Americans is not known. Internationally, MM accounts for 0.8% of all cancer deaths with approximately 86,000 new cases per year. The current 5-year survival for a patient newly diagnosed with MM in the United States was 33% (data from 1996 to 2002), up from 26% 30 years ago. In patients treated on clinical trials, the median survival is approximately 50 %. **(Parkin, 2002)**

Over the past 5 years, significant progress has been made in the diagnosis and assessment of patients with MM. Significant advances include a simplified staging system, an updated uniform international response criteria; the development of a sensitive new serum test to detect free light chain production (free light chain assay); the recognition of specific adverse cytogenetic abnormalities; and the evolution of genomics, which will identify specific and targeted therapies for individual MM patients. For the first time in decades, major therapeutic advances have been implemented in the treatment of MM patients. These include 2 new classes of agent: immunomodulatory drugs and proteosome inhibitors. In addition, clinical trials have solidified the role of hematopoietic stem cell transplant and established the benefits of post-transplant maintenance therapy. Finally, a number of new agents are in development that specifically targets the myeloma cells and/or the bone marrow microenvironment. These advances have resulted in expanded treatment options, prolonged disease control and survival, and improved quality of life for patients with MM **(Kyle, 2003)**

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