Advances in the Biology and Treatment of Multiple Myeloma

James R. Berenson, MD and Robert A. Vescio, MD

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INTRODUCTION

Multiple myeloma is the second most common hematologic malignancy, with approximately 15,000 new cases each year in the United States. Our understanding of the pathophysiology underlying myeloma continues to expand, but the etiology of this plasma-cell dyscrasia remains unclear. Although controversy remains regarding a possible viral etiology of myeloma, evidence suggesting a role for the human herpesvirus-8 (HHV-8) is mounting. The roles of cytogenetic abnormalities, as well as aberrant angiogenesis and cytokine expression in the etiology of myeloma continue to be explored, and may lead to future therapeutic strategies. Transplantation in myeloma is rarely curative, but offers clinical benefit for young and possibly older myeloma patients as well. Newer bisphosphonates may offer greater ease of administration, improved efficacy, and possibly even enhanced anti-tumor effect. Finally, thalidomide and other new agents offer new therapeutic alternatives to myeloma patients who were previously refractory to multiple agents.

Multiple myeloma accounts for approximately one-tenth of all hematologic malignancies, and its incidence is rising as our society ages. Multiple myeloma is a malignant plasma-cell dyscrasia (mature B-cell lymphoid neoplasm), character-
ized by the accumulation of malignant plasma cells in the bone-marrow compart-
ment. These terminally differentiated B-lymphocytes produce a single immuno-
globulin (Ig) known as a monoclonal protein. Monoclonal proteins are the
laboratory hallmark of multiple myeloma, and are also seen in other disorders
such as monoclonal gammopathy of undetermined significance and Walden-
strom's macroglobulinemia. Although we continue to add to our understanding
of the pathophysiology underlying myeloma, the etiology of this plasma-cell
dyscrasia remains unclear. Controversy surrounds the possible viral etiology of
myeloma, yet evidence suggesting a role for HHV-8 is mounting. There is also
increasing understanding of the role of genetic abnormalities, angiogenesis, and
cell-signaling pathways in this B-cell malignancy. These developments have
resulted in exciting new therapeutic options for patients with this disease. These
novel therapeutic approaches are clearly needed, because the median survival of
myeloma has not improved during the past several decades. High-dose therapy
followed by hematopoietic support for patients with myeloma is rarely curative,
but offers some clinical benefit, and now can be safely performed even for
patients in their seventies. Bisphosphonates have become part of the standard of
care for bone disease and hypercalcemia in myeloma, but newer analogs may
offer greater ease of administration, improved efficacy, and possibly even an
enhanced anti-tumor effect. In addition, our fundamental understanding of the
pathophysiology of bone disease in these patients has changed dramatically, and
is leading to new therapeutic approaches. Thalidomide offers significant clinical
benefit to myeloma patients who were previously refractory to multiple agents,
and its role in early stages of the disease is under investigation. A multitude of
other new promising drugs are also in early clinical trials.

BIOLOGY

The Malignant Cell of Origin

The predominant cell type in the bone marrow of patients with multiple
myeloma has the characteristics of a plasma cell (1). However, these cells have
a low proliferative rate and have generally been unable to sustain tumor growth
in vivo. These observations suggest that there are other myeloma precursor cells
that are responsible for proliferation of the malignant popu-Iation (2,3). The
presence of such cells could also explain the observation that the malignant
plasma cells appear to be restricted to the microenvironment of the bone marrow,
although the disease is widely disseminated throughout the axial skeleton.

Because of the monoclonal nature of the immunoglobulin (Ig) synthesized by
the malignant cells, the genes responsible for the production of this protein can
be used as molecular markers. Furthermore, characteristic changes in these genes
occur at different stages of B-cell differentiation, permitting identification of the
cell types in this lineage that are part of the tumor clone (3–6). It has been
proposed that the abnormal B-cells originate in the lymph nodes, and then