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Multiple Myeloma

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Molecular Pathogenesis of Multiple Myeloma 985
Giovanni Tonon

Several genetic mechanisms underlying the pathogenesis of multiple myeloma have been elucidated in the past decade. In particular, the presence of two distinct karyotypic patterns, that identify two patient groups and drive different pathogenetic and prognostic paths in the development of myeloma, have been identified, and the role of reciprocal chromosomal translocations and cyclin dysregulation have been identified. Despite this progress, several questions of critical importance remain to be addressed for the understanding of the pathogenesis of multiple myeloma. For example, little is known about the role of the primary events, including cyclin D overexpression and multiple myeloma set domain activity in the early pathogenesis of the disease. The additional lesions that promote the evolution of monoclonal gammopathy of undetermined significance to multiple myeloma (MM) and, within MM, the progression toward a more aggressive and proliferative disease is only starting to emerge. The heterotypic relationship between the stroma and the MM plasma cells also has not been fully explored. The understanding of the biology of MM cancer stem cells and of the pathways driving their maintenance, proliferation, and differentiation is still in its infancy. Recent and ongoing high-resolution genomic studies are leading the way toward a more refined and conclusive understanding of this disease.

The Role of the Bone Marrow Microenvironment in the Pathophysiology of Myeloma and Its Significance in the Development of More Effective Therapies 1007
Constantine S. Mitsiades, Douglas W. McMillin, Steffen Klippel, Teru Hideshima, Dharminder Chauhan, Paul G. Richardson, Nikhil C. Munshi, and Kenneth C. Anderson

Multiple myeloma (MM) is viewed as a prototypic disease state for the study of how neoplastic cells interact with their local bone marrow (BM) microenvironment. This interaction reflects not only the osteotropic clinical behavior of MM and the clinical impact of the lytic

bone lesions caused by its tumor cells but also underlines the broadly accepted notion that nonneoplastic cells of the BM can attenuate the activity of cytotoxic chemotherapy and glucocorticoids. This article summarizes the recent progress in characterization, at the molecular and cellular levels, of how the BM milieu interacts with MM cells and modifies their biologic behavior.

Pathophysiology of Multiple Myeloma Bone Disease **1035**
Suzanne Lentzsch, Lori A. Ehrlich, and G. David Roodman

Multiple myeloma is a plasma cell malignancy characterized by the frequent development of osteolytic bone lesions. The multiple myeloma–induced bone destruction is a result of the increased activity of osteoclasts that occurs adjacent to multiple myeloma cells. This activity is accompanied by suppressed osteoblast differentiation and activity, resulting in severely impaired bone formation and development of devastating osteolytic lesions. Recently the biologic mechanism involved in the imbalance between osteoclast activation and osteoblast inhibition induced by multiple myeloma cells has begun to be clarified. In this article, the pathophysiology underlying the imbalanced bone remodeling and potential new strategies for the treatment of bone disease in multiple myeloma are reviewed.

Mouse Models of Human Myeloma **1051**
Constantine S. Mitsiades, Kenneth C. Anderson, and Daniel R. Carrasco

Multiple myeloma (MM) remains incurable despite high-dose chemotherapy with stem cell support. There is need, therefore, for continuous efforts directed toward the development of novel rational-based therapeutics for MM, which requires a detailed knowledge of the mutations driving this malignancy. In improving the success rate of effective drug development, it is equally imperative that biologic systems be developed to better validate these target genes. Here we review the recent developments in the generation of mouse models of MM and their impact as preclinical models for designing and assessing target-based therapeutic approaches.

Preclinical Studies of Novel Targeted Therapies **1071**
Teru Hideshima and Kenneth C. Anderson

The bone marrow (BM) milieu confers drug resistance in multiple myeloma (MM) cells to conventional therapies. Novel biologically based therapies are therefore needed. Preclinical studies have identified and validated molecular targeted therapeutics in MM. In particular, recognition of the biologic significance of the BM microenvironment in MM pathogenesis and as a potential target for novel therapeutics has already derived several promising approaches. Thalidomide, lenalidomide

(Revlimid), and bortezomib (Velcade) are directed not only at MM cells but also at the BM milieu and have moved rapidly from the bench to the bedside and United States Food and Drug Administration approval to treat MM.

Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma **1093**
Robert A. Kyle and S. Vincent Rajkumar

In 1978, the term "monoclonal gammopathy of undetermined significance" (MGUS) was introduced. MGUS is defined as a serum monoclonal (M) protein less than 3.0 g/dL; less than 10% plasma cells in the bone marrow, if done; little or no M protein in the urine; and absence of lytic bone lesions, anemia, hypercalcemia or renal insufficiency. This article discusses the recognition, prevalence, natural history, and progression of MGUS. Management of the disease is discussed along with its association with other disorders. Information on smoldering multiple myeloma is included.

Prognostic Factors and Staging in Multiple Myeloma **1115**
Rafael Fonseca and Jesus San Miguel

The field of multiple myeloma prognostication is replete with studies that have shown the value of independent predictors in determining clinical outcome. It is clear that host factors and factors intrinsic to the cells are the ultimate determinants of prognosis. In the immediate period after diagnosis, those factors related to the host are likely to be more relevant, whereas with passing time factors intrinsic to the cells predominate. At a minimum, we recommend that a comprehensive molecular cytogenetic assessment be performed at diagnosis, together with conventional evaluation, including β_2-microglobulin and albumin. In addition, information on proliferative activity of plasma cells may be of value. The introduction of novel methods of prognostication should be strongly considered in all clinical trials.

Management of Newly Diagnosed Myeloma **1141**
S. Vincent Rajkumar and Antonio Palumbo

The treatment of multiple myeloma has changed dramatically in the last decade with the introduction of thalidomide, bortezomib, and lenalidomide. Patients eligible for autologous stem cell transplantation (ASCT) are treated with non-alkylating agent–containing regimens as initial therapy; typically thalidomide-dexamethasone or lenalidomide-dexamethasone. For patients not eligible for ASCT, the current standard of care is melphalan, prednisone, and thalidomide. Ongoing trials will soon assess if combinations including melphalan and prednisone plus bortezomib or MP plus lenalidomide may be considered an attractive option. Patients who have risk factors, such as deletion 13 or

translocation t(4;14) or t(14;16), are candidates for novel, more aggressive treatments.

Role of Stem Cell Transplantation **1157**
Jean-Luc Harousseau

Hematopoietic stem cell transplantation (SCT) was introduced in the treatment of multiple myeloma in the 1980s. In the autologous setting, the use of peripheral blood stem cells instead of bone marrow has markedly improved feasibility. In fit patients who have normal renal function and are younger than 65 years of age, randomized studies have shown the superiority of autologous stem cell transplantation (ASCT) compared with conventional chemotherapy. ASCT is now considered the standard of care in this population of patients. It is currently challenged, however, by the introduction of novel agents, such as thalidomide, bortezomib, and lenalidomide. The role of allogenic SCT remains controversial, even with reduced intensity conditionings. Prospective studies still are needed to evaluate the impact of both autologous and allogeneic SCT in this new era.

Management of Relapsed and Relapsed Refractory Myeloma **1175**
Efstathios Kastritis, Constantine S. Mitsiades, Meletios A. Dimopoulos, and Paul G. Richardson

Studies of bortezomib, thalidomide, and lenalidomide have shown promising clinical activity in relapsed/refractory multiple myeloma (MM). Bortezomib alone and in combination with other agents is associated with high response rates, consistently high rates of complete response, and a predictable and manageable profile of adverse events. Thalidomide-based regimens have also shown substantial clinical activity. The accumulating experience from ongoing trials of bortezomib/lenalidomide/dexamethasone combinations in patients who have relapsed/refractory or newly diagnosed MM will provide critical information that will determine the possible role of this combination as the basic backbone for combination regimens for management of advanced MM.

Immune Therapies **1217**
Rao H. Prabhala and Nikhil C. Munshi

Immune cells with specific functions and abilities are vital to cancer treatment prevention. Although there have been many accomplishments made in the areas of immunotherapy and immunobiology of myeloma, there are still many obstacles in the way of conceptualizing the interrelationships between immune cells and tumor cells. To provide better understanding of these concepts and to move toward improved

therapies for myeloma, cell-based therapeutic approaches should be developed.

Complications of Multiple Myeloma **1231**
Joan Bladé and Laura Rosiñol

Multiple myeloma, also known as myeloma or plasma cell myeloma, is a progressive hematologic disease. Complications of multiple myeloma include renal insufficiency, hematologic complications (anemia, bone marrow failure, bleeding disorders), infections, bone complications (pathologic fractures, spinal cord compression, hyercalcemia), and neurologic complications (spinal cord and nerve root compression, intracranial plasmacytomas, leptomeningeal involvement, among others). This article reviews these various complications connected to multiple myeloma, examining their various causes and possible treatment.

Complications of Myeloma Therapy **1247**
Angela Dispenzieri

The advent of new therapies for multiple myeloma brings new hope for patients but also new side effects. Emerging information about the risks of supportive care therapies, including long-term, high-intensity bisphosphonate use and erythropoiesis-stimulating agents, is examined. As the number of drugs in the myeloma armamentarium grows, so does the list of possible side effects and interactions. With current progress, not only are there more complications to consider but patients are also living longer and the risk for delayed complications is becoming more relevant. The author provides perspective about the risks for the most active and commonly used single-agent and combination myeloma therapies.

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