Targeted Therapy in Multiple Myeloma

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Abstract

Multiple myeloma is a plasma cell malignancy that is incurable with existing conventional and/or high-dose chemotherapy. However, increased understanding of the molecular pathogenesis of myeloma has allowed for the development of novel targeted approaches based on identification of genetic and signaling pathway abnormalities and interaction between multiple myeloma cells and their microenvironment in the development, progression, and drug resistance and bone disease of multiple myeloma. These studies were rapidly translated from the bench to the bedside as clinical applications, including the use of thalidomide and its more potent multiple myeloma immunomodulatory analogues (IMiDs): lenalidomide, the proteasome inhibitor bortezomib, and arsenic trioxide (As$_2$O$_3$). Furthermore, numerous agents directed to both multiple myeloma cells and the bone marrow microenvironment, including farnesyltransferase inhibitors, histone deacetylase inhibitors, Bcl-2 antisense oligonucleotide, heat shock protein inhibitors, and inhibitors of vascular endothelial growth factor (VEGF) or its receptor and inhibitors of insulin-like growth factors and their receptor (IGF-1R) have also been identified and are in early clinical trials. Furthermore, genomics, proteomics, and cell signaling studies have provided the rationale for incorporating these novel agents into existing therapies or into a targeted therapy approach in combination. In the future, these approaches will improve outcomes of patients with multiple myeloma, overcome drug resistance, and finally change the natural history of this disease.

Key Words: Multiple myeloma, Molecular pathogenesis, Microenvironment, Targeted therapy
1. INTRODUCTION

Multiple myeloma (MM) is a malignant plasma dyscrasia characterized by excessive numbers of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD, IgE) or Bence-Jones protein (free light chains) (1). In the United States, the estimated incidence of MM in 2006 is 16,570, with approximately 11,310 deaths (http://www.leukemia-lymphoma.org/attachments/National/br_1152629053/). Despite the use of conventional or intensive chemotherapy followed by stem cell transplantation, classic cytotoxic agents cannot suppress the inevitable relapses of this tumor, and myeloma remains incurable. Recent advances in the understanding of the mechanisms that mediate MM cell homing, proliferation, survival, drug resistance, and bone disease have facilitated the development of novel targeted approaches. Insight into intracellular signaling pathways as well as interactions in the MM cell–host bone marrow microenvironment through cell adhesion molecules and the secretion of cytokines has identified multiple novel therapeutic targets. Importantly, identification of genetic changes associated with progression of monoclonal gammopathy of unclear significance (MGUS) to MM will provide novel therapeutic targets as well as stratify patients who have diverse risk and prognostic implications. Novel targeted agents, especially those used in combination to improve patient outcome and overcome drug resistance, represent the future of MM therapy. In this chapter, we describe recent data obtained from laboratory research as well as the clinical utility of targeted therapy approaches in multiple myeloma.

2. MOLECULAR PATHOGENESIS OF MULTIPLE MYELOMA

Multiple myeloma is a clonal plasma cell neoplasm of transformed plasmablasts with somatic hypermutation and immunoglobulin H (IgH) switching during B-cell development in the germinal center or transformed terminally differentiated plasma cells in the bone marrow (2). MM can be preceded by several premalignant stages, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma. The application of extensive molecular, cytogenetic, and chromosomal comparative genomic hybridization (CGH) techniques have identified sequential genetic changes during MGUS progression to MM and those that lead to further progression to plasma cell leukemia (PCL) (3–6). Moreover, it has been demonstrated that most of the gradual changes in gene expression were in the transformation of normal cells to MGUS plasma cells, with only a relatively small list of differentially expressed genes being perturbed in the progression of MGUS to MM (4). These findings improved DNA-based classification by delineating distinct prognostic implications and the ability to provide new therapeutic targets in MM. Attempting to better understand this multistep transformation process, Davies et al. defined the differentially expressed genes in MM by different functional groups, including oncogenes/tumor-suppressor genes, cell-signaling genes, DNA-binding and transcription factor genes, and developmental genes (4) (Fig. 1).

Nearly all MGUS and MM patients have numeric and/or structural chromosome abnormalities (7). Two major subtypes of ploidy categories characterize MM: hyperdiploid and nonhyperdiploid. The biologic basis of hyperdiploid MM involves multiple trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21, whereas nonhyperdiploid MM is associated with primary IgH translocations at the 14q32 locus (5,8). At present, the ploidy categories of myeloma can be detected by karyotype analysis, intracytoplasmic immunoglobulin fluorescence in situ hybridization (clg-FISH), gene expression profiling, or the proliferation index...