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The Evolution of Targeted Therapy: Novel Agents for Multiple Myeloma

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Introduction

Multiple myeloma (MM) is a malignant neoplasm characterized by the accumulation of clonal plasma cells in the bone marrow, which leads to skeletal destruction, renal failure, hypercalcemia, and anemia.¹ MM is typically chemosensitive at initial diagnosis, but response duration becomes progressively shorter with successive treatments.² Treatment of MM has improved dramatically over the past several years. The 5-year survival rate increased from 25% in 1975 to 34% in 2003; however, the disease remains incurable.³

In addition to genetic lesions intrinsic to MM cells, the bone marrow microenvironment plays a critical role in the development, maintenance, and progression of MM. Direct interactions occur between MM cells and bone marrow stromal cells (BMSCs) and between MM cells and extracellular matrix (ECM) proteins. Adhesion-induced signaling and the cytokines and growth factors that are secreted in response to adhesion activate cascades that increase the growth, survival, migration, and drug resistance of MM cells; negatively impact antitumor immunity; and promote tumor angiogenesis.⁴ A recently increased understanding of the bone marrow microenvironment in MM has played an important role in the development of the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide, which have changed the standard of care for patients, leading to improved treatment strategies and survival rates.¹

Clinical Manifestations of MM

The diagnosis of myeloma is not always simple. Careful consideration of the patient's constellation of symptoms is essential. The symptoms of MM may include fatigue, bone pain, easy bruisability, bleeding, and frequent infections, which reflect manifestations of underlying anemia, hypercalcemia, lytic bone lesions, thrombocytopenia, and hypogammaglobulinemia (FIGURE 1).^{1,5} Two-thirds of patients present with bone pain. Lytic lesions, osteoporosis, or fractures are seen in 79% of patients at presentation. Additional clinical features such as weakness, infection, bleeding, and weight loss (>20 lb) are reported in as many as 82%, 13%, 13%, and 24% of patients, respectively.⁵

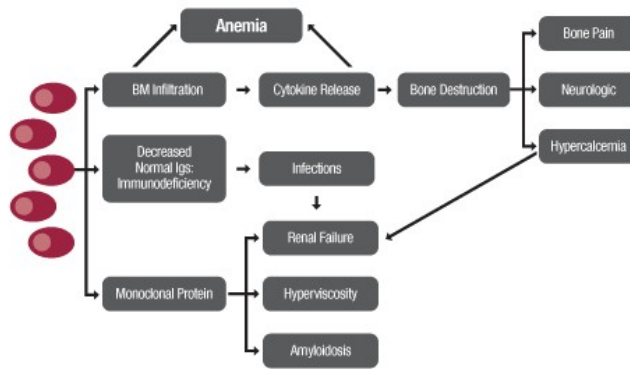


Figure 1

Clinical manifestations of multiple myeloma and biological cause of individual symptoms.
Adapted from Jagannath.¹

Development of Bone Disease

Osteolytic lesions secondary to bone resorption are a hallmark of MM. In MM, the processes of bone resorption and formation are uncoupled. There is concomitant upregulation of factors that stimulate osteoclast formation and function, as well as suppression of negative regulators of osteoclastogenesis and/or positive regulators of bone formation.^{6,7} This process often leads to hypercalcemia, lytic bone lesions, and bone pain, which is present in two-thirds of patients with MM.⁵ Bisphosphonates have been shown to reduce the number of skeletal events related to MM.⁵

Increased expression of the receptor activator of nuclear factor-kappaB (NF- κ B) ligand (RANKL) and its binding to RANK on osteoclasts leads to osteoclast activation and bone destruction. Osteoblast production of osteoprotegerin (OPG), a soluble decoy receptor for RANKL that normally interferes with osteoclast activation, is reduced in myeloma, further enhancing osteoclast activation and bone resorption. Myeloma cells also have the ability to upregulate the expression of RANKL, in part by the release of macrophage inflammatory protein-1 α .⁶

Targeting the RANKL-RANK axis with OPG in preclinical models of MM has been shown to inhibit the development of cancer-induced bone destruction and to interfere indirectly with MM proliferation via its negative effect on osteoclast development.⁸ Denosumab, a fully human anti-RANKL monoclonal antibody, has been shown to be effective at rapidly decreasing bone resorption for a sustained period⁹; it is currently being evaluated in clinical trials as therapy for MM-related skeletal events.

MM cells also produce Dickkopf-1 (DKK-1), which inhibits maturation of osteoblasts and suppresses osteoblast production of OPG, while enhancing expression of RANKL. Levels of DKK-1 correlate with focal bone lesions in patients with MM. Blockade of DKK-1 in murine models of myeloma inhibits the development of osteolytic lesions and reduces MM proliferation in the context of the bone marrow microenvironment.^{7,10} Anti-DKK-1 therapeutics are also currently in clinical development.

Development of Anemia

Anemia is present in up to 72% of patients at diagnosis, and most patients with MM will experience anemia at some point during the course of their disease. The cause of anemia in myeloma is multifactorial.⁵ Renal insufficiency due to cast nephropathy, hypercalcemia, and circulating inflammatory cytokines (eg, tumor necrosis factor [TNF] α and interleukin [IL]-1) may lead to low endogenous erythropoietin levels. In addition, studies have shown an apoptotic effect of myeloma cells on red blood cell precursors and an impact on erythroid colony formation.¹¹ For some patients, anemia is related to direct myeloma cell infiltration and replacement of the bone marrow; in others, hemoglobin correlates specifically with the percent of myeloma cells in S phase, suggesting that the bone marrow cytokine milieu that is permissive for myeloma cell proliferation is not conducive to effective erythropoiesis.⁵ Furthermore, anemia can be a result of "impaired iron utilization" due to increased production of hepcidin, a liver-produced peptide hormone. Hepcidin binds to the cell membrane iron exporter ferroportin and induces internalization and degradation, resulting in diminished iron flow into plasma and restricted delivery of iron into maturing erythrocytes. IL-6, which is often increased in patients with myeloma, may play an important role in the anemia of MM, in part through upregulated expression of hepcidin.¹¹ Ongoing clinical studies of the anti-IL-6 monoclonal antibody CNTO 328 in MM will help further elucidate the role of IL-6 in the anemia of MM.¹²

Interaction Between MM Cells and Bone Marrow Microenvironment

Interactions between MM cells and accessory BMSCs, and between MM cells and ECM proteins in the bone marrow milieu, play a crucial role in MM pathogenesis. Several proteins are involved in direct MM cell-ECM/stromal interactions, including very late antigen (VLA)-4 and intercellular adhesion molecule (ICAM)-1.¹³ The consequent production of various cytokines leads to activation of signaling pathways mediating growth, survival, drug resistance, the migration of MM cells, osteoclastogenesis, and angiogenesis.

A broad spectrum of intracellular proliferative and antiapoptotic signaling pathways are activated in MM cells as a result of the contact between these cells and structural and cellular constituents in the microenvironment and the upstream binding of cytokines to their receptors. The functional sequelae include signaling through the PI-3K/Akt/mTOR cascade, the Ras/Raf/MAPK pathway, the JAK/STAT3 pathway, and the IKK- α /NF- κ B pathway (FIGURE 2).¹⁴ Activation of these signaling pathways leads to the transcription of genes that play a critical role in MM pathogenesis, chemoresistance, proliferation, and survival.^{15,16}

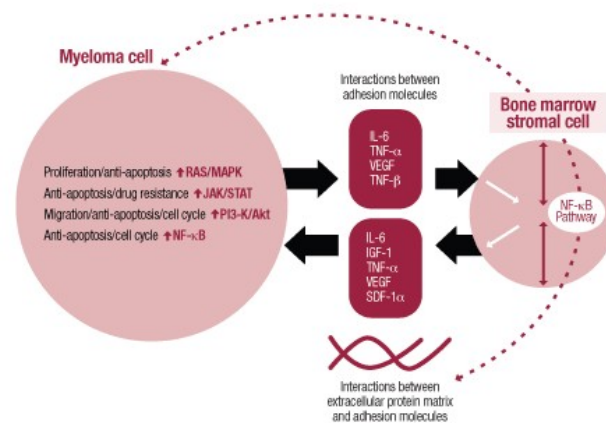


Figure 2

Interaction of myeloma cells with the bone marrow microenvironment.
Adapted from Ching et al.¹⁴

Cell adhesion induces drug resistance, cell cycle arrest, apoptosis inhibition, and protection from drug-induced DNA damage.

The soluble MM cell-growth factors that are liberated as a result of MM cell/BMSC interaction include IL-6, insulinlike growth factor-1 (IGF-1), stromal-derived factor-1 (SDF-1), and vascular endothelial growth factor (VEGF). Some of these growth factors stimulate the proliferation of MM cells, induce overexpression of antiapoptotic proteins Bcl-xL and Mc1-1, and inhibit CD95 (Fas)-induced apoptosis, thereby promoting their resistance to drug-induced apoptosis.^{13,15}

- IL-6 is produced by MM adherence to BMSCs; this and other cytokines mediate MM cell growth, survival, and drug resistance.¹⁷ IL-6 confers resistance to dexamethasone via PI3-K/Akt signaling, and it protects against dexamethasone-induced apoptosis via inactivation of caspase-9.¹⁷ In addition, IL-6 inhibits the antigen-presenting function of dendritic cells by blocking dedifferentiation of monocytes to dendritic cells, thereby contributing to the immune deficits characteristic of MM.¹³
- IGF-1 induces proliferation and survival of MM cells, as well as drug resistance, via MEK/ERK and PI3-K/AKT signaling cascades. It also triggers phosphorylation and inactivation of forkhead transcription factor and upregulates intracellular antiapoptotic proteins including FLICE-inhibitory protein, survivin, cellular inhibitor of apoptosis protein-2, A1/Bfl-1, and XIAP.¹⁷
- VEGF accounts for some of the increased angiogenesis seen in the bone marrow of patients with MM. VEGF induces modest proliferation and pronounced migration of MM cells via the MEK/MAPK and PI3-K/PKC signaling pathways, respectively.¹³
- TNF- α activates NF- κ B and upregulates expression of adhesion molecules (VLA-4 and lymphocyte function-associated antigen-1) on MM cells and their ligands (vascular cell adhesion molecule [VCAM]-1 and ICAM-1) on BMSCs, resulting in greater binding of MM to BMSCs and associated induction of cell adhesion-mediated drug resistance (CAM-DR) and secretion of additional cytokines (IL-6, IGF-1, VEGF). This in turn promotes MM cell survival and protects MM cells from apoptotic stimuli.¹³
- SDF-1 binds to CXCR4, a chemokine receptor on MM cells. It promotes MM cell homing to the bone marrow and induces secretion of IL-6 and VEGF in BMSCs. It also upregulates VLA-4-mediated MM cell adhesion. SDF-1 promotes proliferation and induces migration and protection against dexamethasone-

Notably, therapeutics targeting MM at many of these levels are in active clinical development.

The Ubiquitin-Proteasome Pathway

The ubiquitin-proteasome pathway (UPP) is responsible for the majority of intracellular protein degradation, which in turn regulates transcription stress response and receptor function. The UPP controls the activation of NF-κB, a major transcription factor, by regulating degradation of its inhibitor, I-κB.¹⁸ Multiple components of the UPP, including the proteasome itself, are upregulated in the process of malignant transformation of a plasma cell, suggesting that its function is crucial for MM pathogenesis. The key steps in the UPP are depicted in **FIGURE 3**.¹⁸

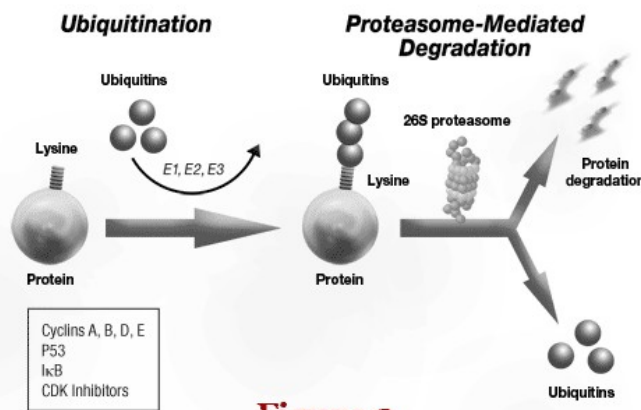


Figure 3

In the ubiquitin-proteasome pathway, polyubiquitinated tails are added to lysine moieties on proteins destined for destruction. Ubiquitinated proteins are degraded by the intracellular 26S proteasome. Rajkumar SV, et al. *J Clin Oncol.* 2005;23:630-639.¹⁸ Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

Mechanisms of Action of Proteasome Inhibitors—Bortezomib: One Target, Multiple Pathways

Bortezomib, the first clinically available reversible inhibitor of the proteasome, has emerged as an important, novel agent for the treatment of MM. It inhibits the chymotrypsinlike activity of the constitutive proteasome present in all cells as well as the immunoproteasome expressed predominantly in cells of hematopoietic origin. Bortezomib is a highly selective and potent proteasome inhibitor ($K_i = 0.6 \text{ nM}$).^{19,20} It has demonstrated activity in preclinical models of MM.²¹ Bortezomib has been shown to overcome MM drug resistance and improve cell sensitivity to other MM therapeutics.^{22,23}

Cytotoxicity from proteasome inhibition involves multiple downstream mechanisms, as described below and summarized in **TABLE 1**.

Table 1. Summary of biologic effects of bortezomib	
Biologic Effects	References
Direct MM cell cytotoxicity by blocking NF-κB activation	(Kropff et al, 2006)
Induction of proteotoxic stress	(Gu et al, 2008)
Inhibition of MM cell/BMSC interactions	(Chauhan et al, 2005)
Inhibition of angiogenesis	(Roccaro et al, 2006)
Potentiation of activity of other cancer therapeutics	(Pagnucco et al, 2004)
Modulation of cell cycle proteins and other pro- and anti-apoptotic pathways	(Orlowski et al, 2005)

BMSC, bone marrow stromal cells; MM, multiple myeloma; NF-κB, nuclear factor-kappa B.

Direct MM Cell Cytotoxicity

Myeloma cells have enhanced NF- κ B signaling compared with normal plasma cells as a result of genetic lesions within the NF- κ B pathway and interactions of MM cells with growth factors in the bone marrow microenvironment. Radiation or chemotherapy activates signaling pathways that result in degradation of I κ B by the UPP, which leads to further increased activity of NF- κ B and may play an important role in inducible chemoresistance.²⁴ Blocking the activation of NF- κ B may decrease the transcription of IL-6, reduce expression of adhesion factors (ICAM, VCAM, e-selectin) necessary for myeloma growth in the bone marrow microenvironment, and reduce expression of angiogenic factors, as depicted in **FIGURE 4**.^{25,26}

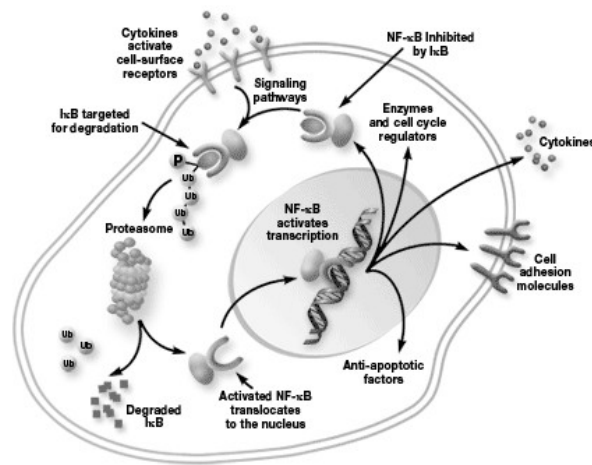


Figure 4

NF- κ B initiates a number of survival pathways. I κ B is degraded by the proteasome, freeing NF- κ B to activate transcription. Reprinted with permission from Richardson et al. *Cell Cycle*. 2005;4:290-296.²⁵

Role of Proteotoxic Stress in Mediating Bortezomib-Induced Cell Death

MM cells produce copious amounts of immunoglobulin (Ig). This abundant Ig production is dependent on sufficient endoplasmic reticulum (ER) and chaperone proteins that allow for proper translation and folding of Ig proteins. Misfolded proteins are degraded by proteasomes. Proteasome inhibition leads to accumulation of misfolded proteins in the ER and, thus, a severe ER stress response and proapoptotic signaling. MM cells may be more sensitive than other cell types to proteasome inhibition. Their abundant production of Ig appears to lower the threshold for induction of the unfolded protein response, resulting in apoptosis.²⁷

Inhibition of MM Cell/BMSC Interactions

Bortezomib acts in the bone marrow microenvironment by inhibiting the binding of myeloma cells to BMSCs, thus inhibiting transcription and secretion of various cytokines, inhibiting NF- κ B, and downregulating growth and antiapoptotic signaling pathways and associated proteins. By inhibiting NF- κ B, bortezomib blocks production of IL-6 and IGF-1, which promote MM-cell survival and resistance to chemotherapy.²⁸

Inhibition of Angiogenesis

Bortezomib has shown greater activity against dividing endothelial cells than against quiescent cells, which suggests that it targets aberrant blood vessel development associated with tumor growth.²⁹ Bortezomib has both direct and indirect inhibitory effects on angiogenesis. The direct effect includes inhibition of proliferation of MM-derived endothelial cells (MMECs) from patients. In vitro and in vivo assays of angiogenesis have demonstrated that bortezomib also negatively impacts MMEC chemotaxis and capillary formation on Matrigel and in chorioallantoic membrane. Indirect effects include dose-dependent inhibition of secretion of factors involved in the autocrine and paracrine growth of MMECs. Bortezomib use results in decreases in VEGF, IL-6, and IGF-1, the expression of which typically increases and persists throughout most of angiogenesis. Decreases in angiopoietin 1 and 2, two growth factors that are mandatory for vessel sprouting and remodeling, are also decreased in response to bortezomib treatment.²⁹

Chemosensitization

Proteasome inhibition potentiates the activity of other conventional cancer therapeutics in part by downregulating innate, inducible, and acquired chemoresistance pathways. Abrogation of NF- κ B-mediated inducible chemoresistance is key to the enhanced therapeutic efficacy of cytotoxic chemotherapy. In addition to targeting cancer cells directly, proteasome inhibitors may overcome drug resistance in vivo by interfering

with the protective interaction between cancer cells and the bone marrow. For example, bortezomib has been shown to downregulate expression of VLA-4 on MM cells, thereby interfering with CAM-DR. Furthermore, bortezomib can overcome the resistance to apoptosis that is conferred by IL-6.²³ These observations suggest that a combination of bortezomib and conventional chemotherapy agents may augment clinical effectiveness and overcome resistance in patients with relapsed refractory MM.¹³

FIGURE 5 summarizes the various activities of bortezomib.

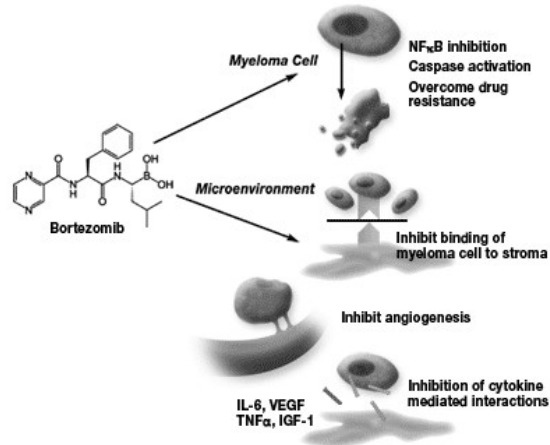


Figure 5

Mechanism of action of bortezomib in myeloma.
Rajkumar SV, et al. *J Clin Oncol*. 2005;23:630-639.¹⁸ Reprinted with permission.
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The Immunomodulatory Drugs

Thalidomide and lenalidomide are two other approved novel antimyeloma agents. Both of these immunomodulatory drugs (IMiDs) have antiangiogenic and immunostimulating effects^{30,31}; however, lenalidomide is a more potent oral thalidomide analog, with greatly enhanced immunomodulatory and antiangiogenic effects in nonclinical studies compared with the parent compound. Three main mechanisms of action of the IMiDs have been identified: direct antitumor effects, indirect antitumor effects by inhibition of the supportive tumor microenvironment, and immunomodulation. Direct antitumor effects occur in part via downregulation of NF-κB signaling and by activation of the intrinsic apoptotic pathway. The IMiDs also downregulate expression of molecules such as ICAM-1, blocking adhesion of MM cells to BMSCs. Furthermore, these drugs impair secretion of IL-6, IGF-1, and VEGF that typically occurs in response to MM adhesion to bone marrow stroma. The immunomodulatory mechanism includes the ability to promote the cytotoxic activity of natural killer and T cells against myeloma cells by stimulating their proliferation and the secretion of IL-2 and interferon gamma.^{31,32} **FIGURE 6** provides a visual depiction of the sites of activity of the IMiDs.³¹

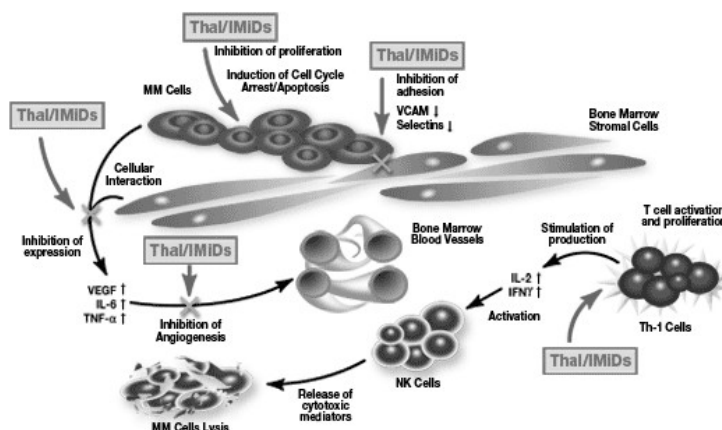


Figure 6

Sites of activity of thalidomide and IMiDs in the bone marrow of patients with multiple myeloma.
Reprinted with permission from Teo. *AAPS J*. 2005;7:E14-E19.³¹ Copyright © 2005 American Association of Pharmaceutical Scientists.

Bortezomib and the IMiDs have changed the management of MM dramatically. Moving forward, there are 34 candidate drugs in the MM pipeline (Phase II and III), of which more than 50% are targeted agents.³³ Several of these therapeutic agents are directed at key targets driving myeloma pathophysiology. **TABLE 2** provides a summary of some of the key drugs in development.

Table 2. Drugs in development that target pathways in multiple myeloma pathogenesis

Target	Pipeline Drug	Company	Phase
HSP90 heat shock protein inhibitors	Tanespimycin	Kosan Biosciences/BMS	III
Histone deacetylase inhibitors	Vorinostat	Merck	III
	ITF 2357	Italfarmaco	II
	Romidepsin	Astellas Pharma/Gloucester Pharma	II
	Panobinostat	Novartis	I/II
Proteasome inhibitors	Carfilzomib	Proteolix	II
VEGF antagonists	Bevacizumab	Genentech/Chugai Pharmaceutical, Roche	II
	Afibercept	Regeneron/Bayer, sanofi-aventis	II
	Sorafenib	Onyx Pharmaceuticals/Bayer	II
	Pazopanib	GSK	II
AKT protein kinase inhibitors	Perifosine	AETerna Zentaris/Keryx Biopharmaceuticals	II
TNF antagonists	Pomalidomide	Celgene	II
RANKL inhibitors	Denosumab (supportive care)	Amgen/Daiichi Sankyo	II
IL-6 inhibitors	CNTO 328	Centocor	II

Data from US National Institutes of Health.³³

The Future

The framework has been established for new treatment paradigms that target MM cell-host BMSC interactions and their sequelae within the bone marrow milieu. These new treatment options have the potential to overcome drug resistance and improve patient outcomes. Identifying appropriate combination therapy involving bortezomib or IMiDs will lead to highly effective regimens for treating a variety of malignant conditions in addition to MM. In the future, gene and protein profiling will further enable patient-specific selection of targeted therapies and will provide a framework for development of more potent and less toxic therapy.

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References

- Jagannath S. Pathophysiological underpinnings of multiple myeloma progression. *J Manag Care Pharm.* 2008;14(7 suppl):7-11.
- Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. *Mayo Clin Proc.* 2004;79:867-874.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. 2009. Vol. 1.2010. Available at: www.nccn.org. Accessed November 14, 2009.
- Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. *Lancet.* 2009;374:324-339.
- Dispenzieri A, Kyle RA. Multiple myeloma: clinical features and indications for therapy. *Best Pract Res Clin Haematol.* 2005;18:553-568.
- Edwards CM, Zhuang J, Mundy GR. The pathogenesis of the bone disease of multiple myeloma. *Bone.* 2008;42:1007-1013.
- Roodman GD. Pathogenesis of myeloma bone disease. *Leukemia.* 2009;23:435-441.
- Berenson JR. Advances in the biology and treatment of myeloma bone disease. *Semin Oncol.* 2002;29(6 suppl 17):11-16.
- Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clin Cancer Res.* 2006;12:1221-1228.
- Tian E, Zhan F, Walker R, et al. The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma. *N Engl J Med.* 2003;349:2483-2494.
- Sharma S, Nemeth E, Chen Y-H, et al. Involvement of hepcidin in the anemia of multiple myeloma. *Clin Cancer Res.* 2008;14:3262-3267.
- Voorhees PM, Chen Q, Kuhn DJ, et al. Inhibition of interleukin-6 signaling with CNTO 328 enhances the activity of bortezomib in preclinical models of multiple myeloma. *Clin Cancer Res.* 2007;13:6469-6478.
- Pagnucco G, Cardinale G, Gervasi F. Targeting multiple myeloma cells and their bone marrow microenvironment. *Ann NY Acad Sci.* 2004;1028:390-399.
- Ching WJ, Lau LG, Yusof N, Mow BMF. Targeted therapy in multiple myeloma. *Cancer Control.* 2005;12(2):91-104.
- Mitsiades CS, Mitsiades NS, Munshi NC, Richardson PG, Anderson KC. The role of the bone

microenvironment in the pathophysiology and therapeutic management of multiple myeloma: interplay of growth factors, their receptors and stromal interactions. *Eur J Cancer*. 2006;42:1564-1573.

16. Sampaio MS, Vettore AL, Yamamoto M, Chauffaille MLLF, Zago MA, Colleoni GWB. Expression of eight genes of nuclear factor-kappa B pathway in multiple myeloma using bone marrow aspirates obtained at diagnosis. *Histol Histopathol*. 2009;24:991-997.
17. Hideshima T, Bergsagel PL, Kuehl WM, Anderson KC. Advances in biology of multiple myeloma: clinical applications. *Blood*. 2004;104:607-618.
18. Rajkumar SV, Richardson PG, Hideshima T, Anderson KC. Proteasome inhibition as a novel therapeutic target in human cancer. *J Clin Oncol*. 2005;23:630-639.
19. Adams J, Palombella VJ, Sausville EA, et al. Proteasome inhibitors: a novel class of potent and effective antitumor agents. *Cancer Res*. 1999;59:2615-2622.
20. Krämer I. Bortezomib: a new approach to anticancer treatment. *EJHP-S*. 2005;11:3-10.
21. LeBlanc R, Catley LP, Hideshima T, et al. Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. *Cancer Res*. 2002;62:4996-5000.
22. Hideshima T, Chauhan D, Podar K, et al. Novel therapies targeting the myeloma cell and its bone marrow microenvironment. *Semin Oncol*. 2001;28:607-612.
23. Richardson PG, Hideshima T, Anderson KC. Bortezomib (PS-341): a novel, first-in-class proteasome inhibitor for the treatment of multiple myeloma and other cancers. *Cancer Control*. 2003;10:361-369.
24. Adams J. Development of the proteasome inhibitor PS-341. *Oncologist*. 2002;7:9-16.
25. Kropff M, Bisping G, Wenning D, Berdel WE, Kienast J. Proteasome inhibition in multiple myeloma. *Eur J Cancer*. 2006;42:1623-1639.
26. Richardson PG, Mitsiades C, Hideshima T, Anderson KC. Proteasome inhibition in the treatment of cancer. *Cell Cycle*. 2005;4:290-296.
27. Gu H, Chen X, Gao G, Dong H. Caspase-2 functions upstream of mitochondria in endoplasmic reticulum stress-induced apoptosis by bortezomib in human myeloma cells. *Mol Cancer Ther*. 2008;7:2298-2307.
28. Chauhan D, Hideshima T, Mitsiades C, Richardson P, Anderson KC. Proteasome inhibitor therapy in multiple myeloma. *Mol Cancer Ther*. 2005;4:686-692.
29. Roccaro AM, Hideshima T, Raje N, et al. Bortezomib mediates antiangiogenesis in multiple myeloma via direct and indirect effects on endothelial cells. *Cancer Res*. 2006;66:184-191.
30. Bartlett JB, Tozer A, Stirling D, Zeldis JB. Recent clinical studies of the immunomodulatory drug (IMiD) lenalidomide. *Br J Cancer*. 2005;93:613-619.
31. Teo SK. Properties of thalidomide and its analogues: implications for anticancer therapy. *AAPS J*. 2005;7:E14-E19.
32. Vallet S, Palumbo A, Raje N, Boccadoro M, Anderson KC. Thalidomide and lenalidomide: mechanism-based potential drug combinations. *Leuk Lymphoma*. 2008;49:1238-1245.
33. US National Institutes of Health. ClinicalTrials.gov. Available at: www.clinicaltrials.gov. Accessed November 14, 2009.

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