Multiple Myeloma

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Multiple myeloma is a malignant disease characterized by plasmacytosis, paraprotein production, bone lesions, hypercalcemia, susceptibility to infections, and renal impairment. The underlying pathophysiologic phenomena of the clinical features include suppression of humoral- and cell-mediated immunity, elevation of IL-6, abnormalities of the bone marrow microenvironment, and increased osteoclastic activity. Overwhelming predictors of prognosis include albumin, β2-microglobulin, and chromosomal karyotype. With modern, intensive therapy including autologous hematopoietic stem cell transplantation, the median survival is approximately 5 yr. The disease is incurable and eventually relapses; requiring salvage therapy. The development of newer agents such as thalidomide, bortezomib, and lenalidomide—drugs that interfere with several of the complex pathophysiologic steps—has improved the outlook of relapsed disease significantly. Current studies are directed at exploring the use of these novel agents earlier in the course of therapy, development of newer targeted therapies, and the use of gene expression profiling to individualize therapy.


Multiple myeloma is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow (Figure 1) and, usually, the presence of a monoclonal Ig in the blood and/or urine. It is the second most commonly diagnosed hematologic malignancy with an annual incidence and prevalence in the United States of approximately 15,000 and approximately 45,000, respectively. The incidence is higher with increasing age (median age at diagnosis 67 yr).

Plasma cell disorders encompass a spectrum including monoclonal gammopathy of unknown significance (MGUS), smoldering or indolent myeloma, and symptomatic myeloma, in order of increasing tumor burden. The differences between these are both quantitative and qualitative; MGUS and smoldering and indolent myeloma are very slowly proliferative and relatively stable diseases in contrast to active myeloma.

Although the disease is largely incurable, the past decade has seen dramatic progress in therapy and understanding of its pathophysiology. Since 1998, three new agents with significant anti-myeloma activity (thalidomide, bortezomib, and lenalidomide) have been identified. In contrast, the preceding three decades had been characterized by reliance on two active classes of agents: Alkylating agents (melphalan and cyclophosphamide) and corticosteroids (Figure 2). The median survival from diagnosis of patients with symptomatic disease that requires therapy is approximately 5 yr—an increase from 3 yr or so a decade ago, likely a result of widespread application of high-dosage chemotherapy with hematopoietic stem cell transplantation (HSCT) and new drugs.

The study of the mechanism of action of these agents has brought a new insight into the biology of the disease. In addition, as in other areas of medicine, technological advances in genetic study and bioinformatics have been making significant contributions to the understanding of myeloma. This review focuses on the recent progress in the pathophysiology, diagnosis, and treatment of myeloma.

Pathophysiology

There is a growing realization that the evolution of the disease involves sequential and complex changes in both the malignant cell and in the surrounding bone marrow microenvironment, including bone. The evolution from MGUS to active myeloma seems to be a multistep, stochastic progression that can occur over a few months to decades (1).

The pathogenetic switch or switches that lead to conversion of normal plasma cell populations to MGUS have not been elucidated. The sequence of events that lead to progression from MGUS to active myeloma has been researched intensely with a resultant glimpse into the various genetic abnormalities and the bone marrow microenvironment disturbances that exist in the various stages of progression. Considerable interpatient heterogeneity in these disturbances has been shown to exist, and this has led to proposed new classifications of the disease on the basis of differences in disease biology.

The tools for the study of the cytogentic makeup of myeloma cells mainly have been conventional karyotyping, fluorescence in situ hybridization, and, more recently, gene expres-
sion profiling. There is no characteristic genetic signature that is diagnostic of the disease. However, activation of one of the three cyclin D genes has been shown to be present in nearly all myeloma cases. Almost half of patients with myeloma have translocations that nonrandomly involve the Ig heavy chain locus on chromosome 14q32 and one of five well-defined chromosomal partners: 11q13 (cyclin D1), 6p21 (cyclin D3), 4p16 (fibroblast growth factor receptor 3 and multiple myeloma SET domain), 16q23 (c-maf), and 20q11 (mafB) (2,3). All Ig heavy chain locus translocations except t(11;14) seem to have unfavorable prognosis. Deletions of chromosomes 13 and 17 (17p13; the p53 locus) also are unfavorable. Hypodiploid myeloma also is associated with poorer survival compared with hyperdiploid myeloma.

Bone lesions in myeloma are thought to be a result of imbalance between the two opposing processes: Bone formation by osteoblasts and bone resorption by osteoclasts. Myeloma cells are thought to increase production of pro-osteoclastogenic cytokines such as macrophage inflammatory protein 1 (MIP-1α), parathyroid hormone–related protein (PTHr-P), vascular endothelial growth factor (VEGF), and IL-6. An increase in expression of RANKL (receptor activator of NF-κB ligand) by osteoblasts and a decrease in the level of its decoy receptor osteoprotegerin result in activation of osteoclasts. Levels of dickkopf 1 (DKK-1), an inhibitor of Wnt signaling that inhibits differentiation of osteoblast precursors, also are increased (3,4).

Interactions between the myeloma cell and other cells in the marrow microenvironment, such as stromal cells and hematopoietic stem cells, and also the extracellular matrix activate multiple signaling pathways, resulting in proliferation/apoptosis of the myeloma cell. The autocrine/paracrine survival factors that are involved in these interactions include IL-6, IGF, VEGF, and TNF-α (3). These complex relationships also contribute to drug resistance, and therapeutic strategies that simultaneously target both the malignant cell and the microenvironment are being designed. It is interesting that only 60% of patients with myeloma have bone lesions. In these patients, the resorption of bone seems to be required for fueling disease progression through release of myeloma survival factors. Other patients with myeloma do not develop disease-mediated bone destruction even in advanced stages of the disease. This suggests that the degree of dependence of myeloma cells on the marrow microenvironment is variable.

**Diagnosis and Investigations**

Some patients’ myeloma is diagnosed incidentally because of elevated serum protein levels, but most patients present with symptoms related to anemia, bone lesions, kidney dysfunction, infections, or hypercalcemia. Various blood, urine, bone marrow, and imaging studies are required to diagnose, stage, and monitor the disease and determine prognosis (Table 1). Table 2 shows the diagnostic criteria for myeloma (5). A critical element of making a correct diagnosis is ensuring that plasmacytosis is clonal, particularly when other typical features are not present.

**Classification and Staging Systems**

The time-honored Durie-Salmon staging system (Table 3) correlates well with tumor burden (6). However, the new international staging system (Table 4) (7), based on β2-microglobulin and albumin, correlates better with prognosis. The translocation and cyclin D classification proposed by Bergsagel and Kuehl (8) has five groups that can be distinguished on the basis of recurrent Ig translocations and cyclin D expression. In a recent proposed molecular classification, seven disease subtypes were identified (9). The last two classifications still have
to be validated but seem to have promising prognostic and therapeutic relevance.

**Prognosis**

The international staging system, the translocation and cyclin D classification, and the molecular classification discussed in the previous paragraph seem to correlate with survival. However, the international staging system is most easily applicable practically because of its simplicity. Other investigations that are practically feasible and have been shown to correlate with outcome include karyotype and some biochemical parameters. Cytogenetic abnormalities such as partial or complete deletion of chromosome 13 and t(4;14) indicate high-risk disease. Other adverse features include plasmablastic morphology and elevated lactate dehydrogenase, plasma cell labeling index, and C-reactive protein (10).

**Treatment**

Advances in therapy have resulted in improvement in the survival of patients with myeloma over the years. Without therapy, the median survival of a patient with active myeloma is approximately 6 mo. With oral melphalan-prednisone (MP) therapy, median survival improves to 3 yr. High-dosage therapy with HSCT further improves median survival to 5 yr.
making this the current standard therapy for myeloma. Tandem autologous transplantation is superior to single in selected patients. Now the newer agents, such as thalidomide (11,12), raise a possible challenge to the established approach of ever-more aggressive dose escalation. To maximize chances for prolonged survival, it is important to plan therapy for each patient in a manner that uses all agents appropriately and sequentially without adversely affecting future treatment options. The dilemma that clinical researchers face is whether to go forward with trials that combine all available agents to increase chances of tumor cell kill while increasing the possibility of drug resistance or to reserve new agents for salvage therapy of relapsed and refractory disease.

The treatment of myeloma comprises disease-specific therapy and supportive care. The general principle is to reserve disease-specific therapy for active disease. The new diagnostic criteria for myeloma (Table 2) identify the patients who have active disease, who almost always need therapy. Definitive therapy is required when the patient is symptomatic or when organ dysfunction is present or impending. There is no evidence that starting definitive therapy in patients with smoldering or indolent myeloma improves survival. Patients with Durie-Salmon stage I myeloma also can be watched without antitumor therapy for a period of time. Table 5 summarizes the general management approach to patients with systemic plasma cell dyscrasias.

### Supportive Therapy

Supportive therapy comprises management of hypercalcemia, skeletal complications, anemia, infections, and pain (13). Regular administration of bisphosphonates such as pamidronate (90 mg once a month) or zoledronate (4 mg once a month) in patients with skeletal lesions is important (14). These drugs arrest and reverse the disturbance of balance between bone formation and resorption. Possible direct and indirect (through effect on the bone marrow microenvironment) anti-myeloma activity of these drugs led to their open-ended use in myeloma. However, the potential for renal damage and increasing concern about osteonecrosis of the jaw warrants periodic reassessment of the need for continued bisphosphonates after 2 yr rather than the previous approach of long-term therapy. Any symptoms that involve the jaw should be investigated carefully, and a careful dental evaluation and corrective work should be performed before starting bisphosphonates or early in the course of therapy.

### Disease-Specific Therapy

The current standard approach consists of initial induction therapy, consolidation with high-dosage chemotherapy and autologous HSCT, maintenance therapy, and salvage therapy.

**Initial Therapy.** As HSCT is being used increasingly in myeloma (15,16), the choice of initial therapy is based on whether the patient is a transplant candidate. Patients who are transplant candidates receive induction therapy that does not cause permanent stem cell damage. Patients who are ineligible for HSCT can receive MP or similar therapy. More intensive alkylating agent–based combi-
nations improve response rates without prolonging survival. However, MP and other alkylating agent–based combinations damage normal hematopoietic stem cells, making stem cell collection for HSCT difficult if not impossible and increasing the risk for myelodysplastic syndrome. The complete remission (CR) rate with MP is $5\%$, and the overall response rate is 40 to 50%. The addition of low-dosage thalidomide to MP in elderly patients with myeloma improves response rates and event-free survival (EFS) but increases toxicity significantly compared with MP (17). Longer follow-up is required to assess effect on overall survival (OS).

The usual induction therapy for patients who are eligible for HSCT is based on high-dosage dexamethasone or methylprednisolone. There is no compelling evidence that regimens that combine modestly active intravenous agents with high-dosage dexamethasone are better than dexamethasone alone with its convenience of oral administration (18). Lack of response to induction therapy does not necessarily signify a poor prognosis because subsequent HSCT can result in substantial cytodestruction (19).

Two recent randomized studies suggested that the widespread adoption of thalidomide-containing induction therapy as the new standard may not be beneficial, because the addition of thalidomide results in higher response rates but increases serious toxicity significantly and does not prolong survival. In a study (20) that compared thalidomide-dexamethasone (TD) with dexamethasone alone, overall response with four cycles was significantly higher with TD (63 versus 41%; $P < 0.002$), but CR rates were comparable (4 versus 0%). The incidence of grade 3 to 5 deep vein thrombosis (DVT), rash, sinus bradycardia, neuropathy, and any grade 4 to 5 toxicity within 4 cycles was significantly more common with TD (45 versus 21%; $P < 0.001$). OS was identical during the first 2 yr. In another study (21), patients received intensive induction therapy followed by tandem autotransplantation and posttransplantation consolidation and maintenance, with or without thalidomide. Although CR rates and 5-yr EFS were better with thalidomide (62 and 56%, respectively) than without (43 and 44%, respectively), the 5-yr OS was similar at 65%. Despite comparable salvage therapy, median survival after relapse was only 1.1 yr in the thalidomide group compared with 2.7 yr in the control group ($P < 0.001$) because of resistance to all types of salvage therapy in thalidomide-treated patients. Severe peripheral neuropathy and DVT occurred more frequently with thalidomide.

Therefore, a reasonable approach may be to use single-agent dexamethasone, with consideration being given to the addition of thalidomide if there is no response to dexamethasone. This will minimize toxicity and expense without compromising outcome and likely will reduce the development of resistant disease. DVT prophylaxis is essential if TD is used, although the optimum mode of prophylaxis is unclear. The use of other newer agents, such as bortezomib and lenalidomide, as part of initial therapy currently is investigational, although the combination of lenalidomide and dexamethasone seems to be very active (22).

**High-Dosage Chemotherapy.** High-dosage melphalan with autologous HSCT may be administered as consolidation therapy after induction (early) or as salvage therapy after relapse (late). Two randomized studies showed higher response rates and prolongation of EFS and OS with early HSCT (15,16), whereas one did not (23). Another randomized study showed that deferring HSCT to relapse after initial therapy did not compromise OS, although EFS was shorter compared with early transplantation (24). Quality of life, as measured by the spread adoption of thalidomide-containing induction therapy as the new standard may not be beneficial, because the addition of thalidomide results in higher response rates but increases serious toxicity significantly and does not prolong survival.

**Table 5. Approach to patients with plasma cell dyscrasias**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Monitoring</th>
<th>Supportive Therapy</th>
<th>Disease-Specific Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>Annual</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Smoldering myeloma</td>
<td>Every 2 to 3 mo</td>
<td>Usually none</td>
<td>None</td>
</tr>
<tr>
<td>Indolent myeloma</td>
<td>Every 1 to 2 mo</td>
<td>+ / –</td>
<td>None</td>
</tr>
<tr>
<td>Stage I myeloma$^b$</td>
<td>Every 1 to 2 mo</td>
<td>+ / –</td>
<td>+ / –</td>
</tr>
<tr>
<td>Stages II to III myeloma$^b$</td>
<td>At least once a month</td>
<td>Yes</td>
<td>Yes</td>
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</table>

$^a$MGUS, monoclonal gammopathy of unknown significance.  
$^b$Durie-Salmon.

![Figure 3. Overall and event-free survival of 451 patients who had myeloma and underwent autologous hematopoietic stem cell transplantation after 200 mg/m² melphalan at the Royal Marsden Hospital between 1982 and 2001 (courtesy of Professor Ray Powles).](image-url)
of relapse. Patients eventually underwent a second transplant as therapy for patients who did not achieve at least a very good partial response to the first transplant. Ongoing studies may be able to answer this question definitively; early data from these studies favor tandem HSCT in terms of EFS, but there is no difference in OS yet. The Arkansas group pioneered the approach of tandem autologous HSCT (27). Long-term follow-up of the Total Therapy 1 study from Arkansas shows 10-yr OS and EFS probabilities of 33% at 10 yr; median 6.2 yr) of 451 patients who had myeloma and underwent autologous HSCT after 200 mg/m2 melphalan (33% at 10 yr; median 6.2 yr) of 451 patients who had myeloma and underwent autologous HSCT after 200 mg/m2 melphalan at the Royal Marsden Hospital (Surrey, UK) between 1982 and 2001.

The Arkansas group pioneered the approach of tandem autologous HSCT (27). Long-term follow-up of the Total Therapy 1 study from Arkansas shows 10-yr OS and EFS probabilities of 33 and 15%, respectively (28). Further intensification of the Total Therapy 1 regimen seemed to improve outcome in the Total Therapy 2 study (29), but improvement stemmed from intensified chemotherapy rather than added thalidomide (21).

Whether tandem HSCT is superior to single HSCT remains contentious. The only published, prospective, randomized study showed a doubling of the likelihood of OS and EFS at 6 yr for patients who underwent tandem HSCT (30). In a subgroup analysis, this benefit was confined to patients who did not achieve at least a very good partial response to the first transplant. Ongoing studies may be able to answer this question definitively; early data from these studies favor tandem HSCT in terms of EFS, but there is no difference in OS yet. The similarities in long-term outcome between the Royal Marsden data (Figure 3) and the long-term follow-up for the Total Therapy 1 group may be at least partly because 131 of the Marsden patients eventually underwent a second transplant as therapy for relapse.

Although a proportion of patients are alive disease-free for a decade or longer after HSCT with essentially normal quality of life (“operational cure” [34]), most patients eventually relapse and need salvage therapy. Third and occasionally even fourth cycles of high-dosage chemotherapy have been used in selected patients. Therefore, it is important to collect enough stem cells

Table 6. Drug therapy of myeloma

<table>
<thead>
<tr>
<th>Drug/Combination</th>
<th>Toxicity</th>
<th>Cost</th>
<th>Efficacy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Appropriateness&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial Therapy</td>
<td>Salvage Therapy</td>
<td></td>
</tr>
<tr>
<td>Melphalan-prednisone</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>Inadequate data to support use as initial therapy</td>
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<tr>
<td>Melphalan-prednisone-thalidomide</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>Initial therapy in patients ineligible for HSCT</td>
</tr>
<tr>
<td>Pulse dexamethasone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Initial therapy in patients ineligible for HSCT</td>
</tr>
<tr>
<td>VAD and equivalent&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>Initial therapy in patients eligible for HSCT</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>Initial therapy in patients eligible for HSCT</td>
</tr>
<tr>
<td>Thalidomide-dexamethasone</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Initial therapy in patients eligible for HSCT</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Initial therapy in patients eligible for HSCT</td>
</tr>
<tr>
<td>Bortezomib-dexamethasone</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Initial therapy in patients eligible for HSCT</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Initial therapy in patients eligible for HSCT</td>
</tr>
<tr>
<td>Lenalidomide-dexamethasone</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Initial therapy in patients eligible for HSCT</td>
</tr>
<tr>
<td>Combinations of novel agents</td>
<td>+++</td>
<td>+++</td>
<td>?</td>
<td>+++</td>
<td>Inadequate data to support use as initial therapy</td>
</tr>
</tbody>
</table>

<sup>a</sup>HSCT, hematopoietic stem cell transplantation; VAD, vincristine, doxorubicin, and dexamethasone; +/−, questionable; + to ++ +, increasing magnitude; ?, no data.

<sup>b</sup>Efficacy and appropriateness ratings for salvage therapy assume no previous exposure to that drug/combination or exposure with good response and relapse off therapy with that drug/combination.

<sup>c</sup>VAD equivalents include VAMP (vincristine, doxorubicin, and methylprednisolone), C-VAMP (cyclophosphamide and VAMP), and DVD (pegylated doxorubicin, vincristine, and dexamethasone).

<sup>d</sup>A low rating despite high response rates reflects ongoing clinical trials and lack of any follow-up data.

TWiSTT score (time without symptoms or treatment toxicity), was better in patients who underwent HSCT early. Another recent study that randomly assigned patients to early HSCT or continued standard-dosage chemotherapy with an option to undergo salvage HSCT at relapse showed no benefit for early HSCT in terms of response rates, EFS, or OS (25).

Although a proportion of patients are alive disease-free for a decade or longer after HSCT with essentially normal quality of life (“operational cure” [34]), most patients eventually relapse and need salvage therapy. Third and occasionally even fourth cycles of high-dosage chemotherapy have been used in selected patients. Therefore, it is important to collect enough stem cells...
at the outset for the planned number of transplants as well as for future salvage therapy.

Administration of posttransplantation maintenance therapy may help to delay disease recurrence. The agents used are corticosteroids, IFN-α, and thalidomide. Although the use of maintenance therapy may improve EFS, OS may not be affected beneficially because recurrent disease may not be sensitive to the agent used for maintenance. A greater worry is that recurrent disease may be resistant to other agents as well (21).

Salvage Therapy. The availability of thalidomide (11,12), bortezomib (35,36), and lenalidomide (37,38) has transformed the treatment of myeloma. It now is possible to achieve excellent cytoreduction including CR in patients whose disease relapses after extensive previous therapy and achieve prolonged survival after relapse. The appropriate approach for a patient with relapsed disease depends on previous therapy, including transplantation, response to previous therapy, the nature of the disease, age, organ function, bone marrow function, the availability of an allogeneic donor, and access to clinical trials of investigational agents (39). Table 6 summarizes the activity and the place of various anti-myeloma agents that currently are available for salvage therapy.

**Thalidomide.** Thalidomide as a single agent is effective in approximately one third of patients with relapsed myeloma (11,12). The exact mechanism of action is unknown, but the drug is thought to act directly on plasma cells, on the marrow microenvironment, and through cytokines that affect the growth of plasma cells. Some patients respond to as little as 50 mg of the drug, but most require 200 mg or so. The addition of other agents such as dexamethasone or multiagent chemotherapy improves response rates further and is effective in patients who have not responded to the agents used singly. The main adverse effects are sedation, fatigue, constipation, peripheral neuropathy, autonomic disturbances, and thromboembolic phenomena.

Figure 4 shows the remarkable long-term outcome of the original cohort of patients who had relapsed myeloma and received thalidomide as a single agent initially. Long-term follow-up of the Arkansas Total Therapy 1 study shows longer postrelapse survival for patients whose disease relapsed in the thalidomide era compared with those whose disease relapsed earlier (28), suggesting that the use of thalidomide as salvage therapy, in contrast to its use as initial therapy, does seem to prolong survival.

**Bortezomib.** Bortezomib, an inhibitor of the 26S proteasome (an intracellular organelle that is responsible for protein degradation), also is effective in 25 to 30% of patients with relapsed myeloma (36). For patients with relapsed disease, bortezomib is more effective than dexamethasone (36). Combining bortezomib with other agents that are active in myeloma, such as corticosteroids, thalidomide, and low-dosage melphalan, increases its efficacy. The main adverse effects are thrombocytopenia, gastrointestinal disturbances, and peripheral neuropathy. Bortezomib seems to be particularly effective in patients with light-chain disease and causes rapid cytoreduction that necessitates precautions against tumor lysis syndrome in patients with a high burden of rapidly proliferative disease.

**Lenalidomide.** Lenalidomide is a structural analog of thalidomide but its in vitro biologic actions are more potent than thalidomide. It is remarkably effective in patients with relapsed disease; including those who have failed prior thalidomide and bortezomib (37,38). The combination of lenalidomide and dexamethasone is superior to dexamethasone alone for relapsed disease (38). While the 25 mg dose has been formally explored
(38), the drug is active at doses as low as 5 mg per day (37). The main side effects are myelosuppression, thromboembolic phenomena (particularly in combination with dexamethasone), and skin rash.

Combinations. All of these new agents have been combined with one or more conventional agents with varying degrees of success and toxicity. Similarly, combinations of more than one of the new agents are being studied. Although still investigational, these are reasonable choices in patients who have no other treatment options. To maximize chances for prolonged survival, it is important to plan therapy for each patient in a manner that utilizes all agents appropriately and sequentially without adversely impacting future treatment options (Figure 5).

The Future

Therapeutic options for myeloma have expanded dramatically with new agents that are active both singly and in combination. With several more novel agents in clinical trials, there is hope that outcomes will improve dramatically. Future clinical trials will be designed with rationale based on preclinical drug data and patient selection according to pharmacogenomic profiles, with sophisticated, individualized therapy. Specific experimental agents, approaches, and targets that are being pursued are too numerous to list entirely. However, a few examples include histone deacetylase inhibitors, heat-shock protein-90 inhibitors, VEGF receptor tyrosine-kinase inhibitors, farnesyl transferase inhibitors, and inhibitors of fibroblast growth factor receptor 3.

Acknowledgments

S.S. and J.M. are members of the speakers’ bureau of and consultant to Celgene Pharmaceuticals (manufacturer of thalidomide and lenalidomide) and Millennium Pharmaceuticals (manufacturer of bortezomib).

References


