Multiple myeloma is a disseminated malignancy of monoclonal plasma cells that accounts for 15% of all hematologic cancers. In 2009, an estimated 20,580 new cases will be diagnosed in the United States, and 10,580 Americans will die of this disease. Incidence rates for myeloma (5.3 in men and 3.5 in women) and mortality rates (3.7 in men and 2.5 in women) per 100,000 population have remained stable for the past decade.

**Epidemiology**

**Gender**
Men are affected more frequently than women (1.4:1.0 ratio).

**Age**
The median age at presentation is 70 years, according to most tumor registries, although the median age reported in studies is approximately 66 years.

**Race**
The annual incidence per 100,000 population is 6.6 among white men and 4.1 among white women. Among black men and women, the frequency doubles to 14.3 and 10.0, respectively, per 100,000 population. This racial difference is not explained by socioeconomic or environmental factors and is presumably due to unknown genetic factors.

**Geography**
There is no clear geographic distribution of multiple myeloma. In Europe, the highest rates are noted in the Nordic countries, the United Kingdom, Switzerland, and Israel. France, Germany, Austria, and Slovenia have a lower incidence, and developing countries have the lowest incidence. This higher relative incidence in more developed countries probably results from the combination of a longer life expectancy and more frequent medical surveillance.

**Survival**
The relative survival rate measures the survival of the cancer patients in comparison to the general population to estimate the effect of cancer. The overall 5-year relative survival rate was 37.1% for 1999-2005.

**Etiology and risk factors**
No predisposing factors for the development of multiple myeloma have been confirmed.

**Environment**
Some causative factors that have been suggested include radiation exposure (radiologists and radium dial workers), occupational exposure (agricultural, chemical, metallurgical, rubber plant, pulp, wood and paper workers, and leather tanners), and chemical exposure to formaldehyde, epichlorohydrin, Agent Orange, hair dyes, paint sprays, and asbestos. None of these associations has proven to be statistically significant, and some have been contradicted by negative correlations. The initial report that survivors of the atomic bombings in Japan had an increased risk of developing myeloma has been refuted by longer follow-up. Interactions between multiple myeloma cells and their microenvironment (the extracellular matrix and the bone marrow stroma), allow multiple
myeloma cells to survive, grow, migrate, and resist apoptosis induced by traditional chemotherapies. These effects are partially mediated through adhesion-mediated signalling and partly through various cytokines, including IL-6, vascular endothelial growth factor, insulin-like growth factor 1 (IGF-1), and TNF-α. The molecular signals mediating the proliferative effects include the RAS/RAF/mitogen activated protein kinase (MAPK) pathway, whereas the P13 kinase (P13K/AKT) pathway provides cell survival and drug resistance signals. Improved understanding of these interactions and the molecular mechanisms mediating them has now allowed us to evaluate novel therapies that directly target multiple myeloma cells as well as act on the bone marrow microenvironment.

**Viruses**

A preliminary report in a limited number of patients noted the presence of herpesvirus 8 in the dendritic cells of patients with multiple myeloma. However, further evaluation by a number of investigators has failed to confirm this result. Patients with myeloma also do not appear to have a significant immune response against this virus.

**Cytogenetics**

Karyotypic abnormalities in myeloma are complex, with both numeric and structural abnormalities. DNA aneuploidy is observed in more than 90%; these are predominantly hyperdiploid, with less than 10% being hypodiploid, and carry a poor prognosis. Recurrent nonrandom structural abnormalities have been identified and linked to the pathogenesis and prognosis of myeloma. The immunoglobulin (Ig) heavy-chain gene at 14q32 is frequently involved in translocations with partner chromosomes 4, 6, 8, 11, and 16. The location and oncogenes involved are shown in Table 1. Translocations involving chromosomes 4 and 16 as well as del17p13 (TP53) have been associated with a poor prognosis. Del13q or monosomy 13 is observed in 15% to 20% of patients with conventional cytogenetics and also carries a poor prognosis across standard and high-dose therapies. Interphase fluorescence in situ hybridization (FISH) with a specific probe for chromosome 13q34 (retinoblastoma gene, \([RB1]\)) identifies this abnormality in up to 50% of patients, with a less clear prognostic implication.

**Genetic factors**

Multiple myeloma is not an inherited disease, but there have been numerous reports of multiple cases in the same family. However, a case-control study revealed no significant increase in its incidence among relatives of patients who had multiple myeloma, other hematologic malignancies, or other cancers.

**Monoclonal gammopathy of unknown significance (MGUS)**

Patients with MGUS develop myeloma, macroglobulinemic lymphoma, or amyloidosis at a rate of 1% per year.

**Signs and symptoms**

The clinical features of multiple myeloma are variable. Findings that suggest the diagnosis include lytic bone lesions, anemia, azotemia, hypercalcemia, and recurrent infections. Approximately 30% of patients are free of symptoms and are diagnosed on routine physicals with abnormal laboratory studies, including elevation of serum protein.

**Bone disease**

Bone pain, especially from compression fractures of the vertebral or ribs, is the most common symptom. At diagnosis, 70% of patients have lytic lesions, which are due to accelerated bone resorption. These changes are induced by factors modulating osteoclastic activity and produced by the bone marrow microenvironment and, to a lesser extent, myeloma cells. These factors include interleukin (IL)-1B, tumor necrosis factor (TNF)-α, and IL-6 as well as newly identified factors such as
osteoprotegerin, TNF-related activation-induced cytokine (TRANCE), macrophage inflammatory protein (mip)-1 α, and receptor activator of nuclear factor kappa B (RANK) ligand. Dickkopf (Xenopus laevis) homolog 1 (DKK-1) has been described as a soluble factor produced by multiple myeloma cells inhibiting osteoblastic activity.

Anemia
Normocytic, normochromic anemia is present in 60% of patients at diagnosis. It is due primarily to the decreased production of red blood cells by marrow, infiltration with plasma cells, and the suppressive effect of various cytokines. Patients with renal failure may also have decreased levels of erythropoietin, which can worsen the degree of anemia.

Hypercalcemia
Among newly diagnosed patients, 20% have hypercalcemia (corrected serum calcium level > 11.5 mg/dL) secondary to progressive bone destruction, which may be exacerbated by prolonged immobility. Hypercalcemia should be suspected in patients with myeloma who have nausea, fatigue, confusion, polyuria, or constipation. It may suggest high tumor burden. It should be considered an oncologic emergency and requires prompt treatment with aggressive hydration and use of bisphosphonates, calcitonin, and antimyeloma therapy.

Renal failure
Approximately 20% of patients present with renal insufficiency and another 20% to 40% develop this complication in later phases of the disease. Light-chain cast nephropathy is the most common cause of renal failure. Additional causes include hypercalcemia, dehydration, and hyperuricemia. Less commonly, amyloidosis, light-chain deposition disease, nonsteroidal anti-inflammatory agents taken for pain control, intravenous radiographic contrast administration, and calcium stones may contribute to renal failure. More recently, bisphosphonate therapy has been associated with azotemia.

Infections
Many patients with myeloma develop bacterial infections that may be serious, and infectious complications remain the most common cause of death in myeloma patients. In the past, gram-positive organisms (eg, Streptococcus pneumoniae, Staphylococcus aureus) and Haemophilus influenzae were the most common pathogens. More recently, however, infections with gram-negative organisms, anaerobes, and fungi have become frequent. The increased susceptibility of patients with multiple myeloma to bacterial infections, specifically with encapsulated organisms, has been attributed to impairments of host-defense mechanisms, such as hypogammaglobulinemia, granulocytopenia, decreased cell-mediated immunity, and the prolonged use of steroids.

Screening and diagnosis
No screening measures for multiple myeloma have demonstrated any benefit. The diagnosis usually requires the presence of bone marrow plasmacytosis and a monoclonal
protein in the urine and/or serum (Table 2). One immunoglobulin class is produced in excess, whereas the other classes are usually depressed.

Initial work-up
The initial work-up for patients suspected of having a plasma cell dyscrasia should include:
- CBC with differential count and platelet count
- Routine serum chemistry panel (eg, calcium, blood urea nitrogen, creatinine)
- Bone marrow aspirate and biopsy to assess plasmacytosis
- serum protein electrophoresis and immunofixation to define protein type
- Serum free light chain
- 24-hour urine protein, electrophoresis, and immunofixation
- quantitative serum Ig levels
- skeletal survey (bone scans contribute little since isotope uptake is often low in purely lytic bone disease)
- cytogenetics, including FISH.

The recently available serum free light-chain assay is useful especially in patients with light-chain-only disease, oligo- or nonsecretory myeloma, patients with renal failure, and amyloidosis.

MRI is an excellent tool for evaluation of spinal cord compression/impingement. In addition, MRI identifies generalized marrow signal abnormalities and focal lesions that can be monitored after therapy. Whole-body $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan is becoming more widely used, as it provides details of axial and appendicular skeletal involvement but also identifies extramedullary soft-tissue plasmacytomas presenting as macrofocal lesions. Both MRI and PET/CT are especially useful in staging oligo- or nonsecretory disease.

In addition, additional useful data may be obtained by analysis of such prognostic factors as plasma cell labeling index, ploidy, and analysis of beta-2-microglobulin, serum albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH) levels.

Laboratory and pathologic features

Peripheral blood
The peripheral blood smear may reveal a normocytic, normochromic anemia with rouleaux formation. Plasma cells may also be seen.

Bone marrow
Bone marrow examination usually reveals an increased number of plasma cells. These cells are strongly positive for CD38, CD138, and cytoplasmic immunoglobulin (clg). The majority of myeloma cells also express CD40 and CD56. Myeloma cells are negative for CD5, CD19, and surface Ig (slg) expression. CD20 may be expressed in a subset of myeloma patients often presenting with the
t(11;14) translocation. CD10 expression is generally negative but has sometimes been noted in advanced disease. Monoclonality may be demonstrated by immunoperoxidase staining with κ and λ antibodies.

The pattern of bone marrow involvement in plasma cell myeloma may be macrofocal. As a result, plasma cell count may be normal when an aspirate misses the focal aggregates of plasma cells that are better visualized radiographically or on direct needle biopsy.

**Monoclonal proteins**

The types of monoclonal protein produced are IgG (60%), IgA (20%), IgD (2%), IgE (< 0.1%), or light-chain κ or λ only (18%). Biclonal elevations of myeloma proteins occur in < 1% of patients, and < 5% of patients are considered to have nonsecretory disease, because their plasma cells do not secrete detectable levels of monoclonal Ig.

**Staging and prognosis**

Patients with symptomatic myeloma should be staged using either the Durie-Salmon system at diagnosis or the International Staging System (ISS), which is determined at the time systemic therapy is begun. These two systems are compared in Table 3. The Durie-Salmon staging system better provides information on tumor burden, whereas the ISS staging system better serves as a prognostic indicator. The ISS is easier to use, and it classifies patients correctly regardless of their geographic origin (ie, North America, Europe, or Asia), age (ie, ≥ 65 years vs younger age), or type of treatment (ie, conventional chemotherapy vs high-dose therapy followed by autologous stem cell transplantation). More recent studies have provided evidence that the ISS is reliable in patients managed with thalidomide (Thalomid), bortezomib (Velcade), or lenalidomide (Revlimid).

**Prognosis**

Prognostic indicators may help guide treatment strategy, but the presence of poor prognostic features should not result in initiation of therapy in patients with asymptomatic myeloma. Prognostic factors for risk stratification are well established for conventional chemotherapy. Use of bortezomib and, to some extent, lenalidomide may be able to overcome some features of poor risk.

**Cytogenetic abnormalities**

Chromosomal abnormalities, especially loss of whole chromosome 13 (monosomy) or deletions of parts of chromosome 13 (13q), with hypodiploidy have been associated with inferior survival after both standard chemotherapy and high-dose therapy. Primary translocations involving 14q32 and 6p21 (cyclin D3 [CCND3], 4p16 (fibroblast growth factor receptor 3 [FGFR3]), 16q23 (c-maf proto-oncogene), in multivariate analysis have been shown to be important predictors of poor survival. These cryptic translocations are best detected using FISH.
Beta-2-microglobulin
Serum beta-2-microglobulin level is an important and convenient prognostic indicator. When cytogenetic changes are not studied, beta-2-microglobulin is consistently the most important prognostic indicator on multivariate analysis. As beta-2-microglobulin is excreted by the kidneys, high levels are observed in patients with renal failure; in this setting, the interpretation of an elevated value is unclear.

LDH
High LDH levels also have been associated with plasmablastic disease, extramedullary tumor, plasma cell leukemia, plasma cell hypodiploidy, drug resistance, and shortened survival.

Other indicators
Other indicators of shortened survival include elevated CRP, DNA hypodiploidy, high plasma cell labeling indices, and plasmablastic histology. Patients with DNA hypodiploidy are also less likely to respond to chemotherapy.

Treatment response criteria
Because the criteria for treatment response in patients with multiple myeloma have varied among institutions, response rates have been difficult to compare in the past. In responders, the Bence Jones protein level is reduced more rapidly than is serum myeloma protein because of the rapid renal clearance of light chains.

The CIBMT/EBMT response criteria follow:
Complete response requires all of the following:
• No serum/urine M protein by immunofixation electrophoresis for ≥ 6 weeks
• < 5% plasma cells in bone marrow aspirate
• No increase in the size or number of lytic bone lesions
• Disappearance of soft-tissue plasmacytomas.
Partial response requires all of the following:
• ≥ 50% reduction in serum M protein > 6 weeks
• ≥ 90% reduction in 24-hr urinary light-chain excretion
• ≥ 50% reduction in soft-tissue plasmacytomas.
Minimal response (but ≤ 49%) requires:
• ≥ 25% reduction in serum M protein for > 6 weeks
• ≥ 50%-89% reduction in 24-hour urinary light-chain excretion
• No increase in the size or number of lytic bone lesions.

The more recent Uniform Criteria for response proposed by the IMWG have sought to further refine these criteria by describing a stringent complete response and a very good partial response (> 90% reduction in the serum paraprotein level), as well as further defining progressive disease. Near complete response is another modification of the criteria.

Treatment
Exciting advances in the understanding of tumor biology and microenvironment—and their potential interaction—have helped to identify unique targets for rational therapeutic intervention to enhance outcome, which has not improved with conventional chemotherapy over the past 3 decades. Until recently, only 5% to 10% of patients with multiple myeloma lived longer than 10 years, and cure remains elusive.

Newly diagnosed patients
Chemotherapy
Dexamethasone/thalidomide Thalidomide has been employed alone and in combination with dexamethasone as initial therapy in newly diagnosed patients. When employed alone, response (50% reduction in paraprotein) was observed in 36% of patients; when it was used along with dexamethasone, the response rate was higher (72% and 64% in two studies), including a 16% complete response rate in one study. The results of a randomized ECOG trial showed that the combination of thalidomide and dexamethasone was superior to use of dexamethasone alone (63% vs 41%; P = .001). This combination does not damage stem cells and allows adequate stem-cell collection. A definite increase in thrombotic episodes has been observed with this combination, prompting prophylactic administration of aspirin, coumadin, or low-molecular-weight heparin.
VAD or VDD (vincristine, liposomal doxorubicin [Doxil], and dexamethasone) regimens were widely used in the past as induction therapy before high-dose therapy. Recent randomized trials have confirmed the inferiority of VAD when compared with both thalidomide- and
bortezomib-based regimens, making this an increasingly less attractive combination. **Pulse dexamethasone alone** as initial therapy no longer is recommended. However, brief therapy with pulse dexamethasone may be warranted under special clinical circumstances (eg, renal failure, hypercalcemia, cord compromise requiring radiation therapy, cytopenia) (Table 4).

**MP** The combination of melphalan (Alkeran) and prednisone has been used over the past 30 years, and other combinations of multiple alkylating agents have not been found to be superior to MP. Approximately 40% of patients respond to the MP regimen, with a median remission duration of 18 months and an overall median survival of 3 years. The MP regimen should be avoided in patients considered to be transplant candidates. Currently, MP should be combined with a novel agent, as noted below.

**MP and thalidomide (MPT)** In two large, prospective, randomized trials in patients older than age 65, and a third randomized trial in patients over 75 years of age, MPT has been shown to be superior to MP for response rate as well as progression-free and overall survival. Side effects (including constipation, deep vein thrombosis [DVT], and peripheral neuropathy) were more commonly encountered with thalidomide but were found to be manageable. MPT offers a possible alternative for older people who generally are not candidates for high-dose therapy.

**MP and Velcade (bortezomib; MPV)** Bortezomib is a first-in-class, potent, selective, and reversible small-molecule inhibitor of the proteasome. In a large international, randomized clinical trial, MPV was shown to be superior to MP for response as well as survival endpoints. MPV induced complete remissions in one third of the patients, with an overall response rate of 71% and a 2-year overall survival of > 80%. Such high complete responses previously were never seen in this population of patients, where one-third of the patients were over age 75 years. Adverse side effects (eg, peripheral neuropathy, asthenia, fatigue, diarrhea, and constipation) were more frequently encountered on the bortezomib arm. However, the treatment was well tolerated by most patients, with treatment discontinuation due to toxicity noted in only 14% of patients in both arms, and a treatment-related mortality of 1% with MPV (vs 2% in the MP group).

**Rd (lenalidomide [Revlimid], low-dose dexamethasone) and VD (bortezomib [Velcade], dexamethasone) combinations** Combinations of novel agents with dexamethasone have now been extensively investigated to provide high response rates in newly diagnosed patients. A randomized study performed by ECOG compared lenalidomide with high-dose dexamethasone (Rd; 40 mg/d on days 1 to 4, 9 to 12, and 17 to 20) versus lenalidomide with low-dose dexamethasone (Rd; 40 mg once a week). In this study, the Rd arm had significantly fewer toxicities than did the Rd arm, including a lower rate of early mortality (5% vs 0.5%, respectively) and a reduced incidence of DVT (24% vs 9%, respectively). Responses were superior in the Rd arm; however, the times to progression (27 months) and the overall survivals at 3 years (79%) were identical between the two arms. A select group of patients proceeding to transplant after 4 cycles also had excellent outcomes. Thus, lenalidomide and dexamethasone can be an induction therapy whether or not the patient is likely to undergo high-dose therapy. Stem-cell collection requires use of chemotherapy mobilization. Bortezomib-containing regimens have also been evaluated in newly diagnosed patients. Using the
combination of bortezomib and dexamethasone, Jagannath et al have reported a complete response rate of 18% and an overall response rate of 88% in a phase II study in newly diagnosed patients. Two large, randomized trials have shown that use of bortezomib plus dexamethasone or of VTD (bortezomib [Velcade], thalidomide, and dexamethasone) is an excellent induction regimen pretransplant. These regimens induce rapid tumor cytoreduction; responses attained pre-transplant are additive post-transplant, and patients at risk have had better outcomes following their use. Currently, the combination of RVD (lenalidomide [Revlimid], bortezomib [Velcade], and dexamethasone) is under investigation in newly diagnosed patients; its use has been promising, leading to response rates in excess of 95% and very manageable toxicity.

**High-dose therapy following induction therapy**

High-dose therapy employed after induction therapy improves the response rate as well as event-free and overall survival. The impressive improvement in event-free (median, 28 vs 18 months) and overall survival (57 vs 42 months) reported in a randomized trial (IFM 90) has been confirmed by another large, randomized trial (median overall survival, 54.8 vs 42.3 months; MRC VII). Most of these studies enrolled patients < 65 years old. Older individuals (< age 70) may tolerate high-dose therapy with peripheral stem cell support well and without excess mortality. Moreover, outcome, in terms of event-free and overall survival, is comparable to that in matched cohorts < 65 years old, making older individuals (≥ 65 years old) also candidates for high-dose therapy. More recently, older patients (> 70 years of age) receiving intermediate-dose melphalan (100 mg/m²) with stem cell support have had a better outcome than have matched controls receiving conventional therapy.

A high-dose alkylating agent, most commonly melphalan at 200 mg/m² with peripheral blood stem cell support, is a standard conditioning regimen. Addition of total-body irradiation (TBI) does not improve the outcome but increases morbidity and results in higher mortality. Interestingly, in a randomized study, Fermand et al have confirmed an equivalent survival benefit between up-front high-dose therapy versus high-dose therapy as a salvage regimen at relapse following initial induction therapy.

**Tandem transplants**

The improved outcome reported after tandem transplants in large cohorts of patients in single-institution studies has been confirmed in one mature, randomized study. Seven years after initiation of therapy, the event-free (42% vs 21%) and overall survival (20% vs 10%) rates were superior for patients receiving tandem transplants than for those given single transplants, respectively (IFM 94). Another randomized trial with a shorter follow-up has confirmed the superior event-free survival (median, 34 vs 25 months) for patients receiving tandem transplants when compared with those given single transplants but not in overall survival. Moreover, the added benefit of the second transplant was not seen in a subset of patients with a complete response or a very good partial response (> 90% paraprotein reduction) after the first transplant in either study.

**Radiotherapy**

Higher doses of radiotherapy (40–50 Gy) are employed for local control and cure of solitary plasmacytoma involving bone and extramedullary sites. Lower doses (20–30 Gy) may be employed for palliation of local bone pain from tumor infiltration, pathologic fractures, and spinal cord compression. It should be emphasized that excellent pain relief may be obtained by prompt institution of high-dose corticosteroid therapy, especially in newly diagnosed patients. Radiotherapy should be employed sparingly, as irradiation of multiple sites may impair stem-cell mobilization in patients who are candidates for high-dose therapy. Employment of high doses of radiation to the spine may preclude the subsequent use of TBI as a conditioning regimen for high-dose therapy.

**Remission maintenance**

**Alkylating agents**

Maintenance therapy with alkylating agents has not prolonged survival when compared with no maintenance therapy. This approach is no longer recommended.

**Steroids for maintenance**

Two large, randomized trials have shown that glucocorticoid maintenance prolongs the duration of remission and improves life expectancy. The SWOG used prednisone (50 mg) every other day, whereas the maintenance regimen in the NCI Canada trial contained dexamethasone (40 mg) daily for 4 days every 4 weeks.

**Thalidomide**

Patients responding to thalidomide and achieving maximal response have received lower-dose thalidomide (50–100 mg) with or without added dexamethasone (40 mg for 4 days every month) as
maintenance therapy. In the MPT regimen, continued administration of thalidomide prolongs the duration of remission. The IFM 99-06 study evaluated maintenance therapy with thalidomide plus pamidronate (Aredia) compared with pamidronate alone or with observation only following tandem autologous transplantation. Superior event-free survival and overall survival were reported in the cohort receiving thalidomide plus pamidronate.

**Interferon-α**

Twenty-four randomized trials have investigated interferon-α as maintenance therapy and neither consistent nor significant benefits have been seen. A recent large Intergroup trial also reported no benefit of interferon maintenance therapy after conventional therapy and autotransplantation.

**Novel agents**

Bortezomib is currently under study as a maintenance strategy. In the APEX study, bortezomib administered weekly proved efficacious and was well tolerated in responding patients who had successfully completed initial treatment. Lenalidomide, the potent small-molecule thalidomide analog with immunomodulatory effects, is also under study as maintenance posttransplant, given at a low dose (10 mg/d) and then increased accordingly to a higher dose (15 mg/d) after 3 months in the study with good tolerance reported. Outcome data are pending from this and other trials.

**Refractory and relapsed, refractory disease**

Approximately 10% to 15% of patients with newly diagnosed multiple myeloma are unresponsive to induction therapy. Moreover, virtually all patients who respond initially will relapse.

**Conventional chemotherapy**

Alkylating agents, alone or in combination, have been effective in approximately one-third of patients with VAD-refractory disease. IV melphalan (70–100 mg/m²) and the combination of high-dose cyclophosphamide and etoposide are two examples of such regimens.

**Thalidomide**

Thalidomide has an established role in therapy for refractory/relapsed multiple myeloma, with 30% of patients achieving at least 50% reduction in paraprotein levels. Remissions obtained are durable. In a large cohort of patients with multiple myeloma receiving thalidomide, 2-year event-free survival rates of ~25% have been observed. Initially, thalidomide was employed in a dose-escalating schedule, starting at 200 mg and achieving a maximal dose of 800 mg. Recently, lower doses have been employed in combination with steroids (Table 4).

**High-dose chemotherapy**

High-dose melphalan and stem cell rescue should be offered to patients who have deferred the transplant initially. A randomized trial on early versus late transplantation has shown that an equivalent survival is conferred on patients undergoing salvage compared to early transplantation.

**Novel agents**

**Lenalidomide**

Lenalidomide has greater potency than does thalidomide in preclinical studies and is better tolerated, with less neurotoxicity, somnolence, and constipation. Two large, multicenter, phase III trials of lenalidomide (25 mg daily for 3 weeks with 1 week off) compared dexamethasone with dexamethasone and placebo in patients with relapsed multiple myeloma. In one study, there was significant improvement in response rate (partial response, 59% vs 21%, respectively) and time to disease progression (11.1 vs 4.7 months, respectively) in the cohort receiving the lenalidomide combination; the results of the second study were almost identical. Similar responses were seen in patients relapsing after prior bortezomib or thalidomide exposure. DVT was a significant complication of this combination, occurring in approximately 15% of patients with myelosuppression the other important toxicity.

**Proteasome inhibitors**

A large, multi-institution, phase II trial of the proteasome inhibitor bortezomib (given IV at a dose of 1.3 mg/m² on days 1, 4, 8, and 11 every 21 days) demonstrated remarkable activity in a heavily treated population of patients with relapsed or refractory multiple myeloma, including patients relapsing after transplantation or not responding to thalidomide, with durable responses noted in about 35% (with 10% complete response). Side effects related to the drug were predominantly gastrointestinal (GI) in nature, with neuropathy, fatigue, and reversible cytopenias also noted. Toxicities were generally manageable with supportive care and dose reduction. Patients who did not respond to bortezomib monotherapy (progressive disease after 2 cycles or stable disease after the first 4 cycles) were permitted to receive combination bortezomib and dexamethasone. Combination therapy induced additional responses in 18% of patients (13 of 74). The large, randomized, phase III APEX trial of bortezomib monotherapy compared with high-dose
Dexamethasone enrolled 669 patients with relapsed multiple myeloma. This trial showed significant improvement in the median time to disease progression (6.5 vs 3.6 months, respectively; \( P < .0001 \)) and median overall survival (29.8 vs 23.7 months, respectively; \( P = .027 \)). Response rates to bortezomib as a single agent were impressive at 43%. The most commonly reported adverse events for bortezomib were GI events, fatigue, pyrexia, and thrombocytopenia; for dexamethasone, they were fatigue, insomnia, and anemia. Neuropathy was also an important issue with bortezomib, but it proved generally manageable with dose reduction and schedule change. DVT was very rare, and efficacy in patients with significant renal dysfunction was noted. Finally, encouraging responses were noted in patients with adverse cytogenetics as well as in patients with advanced bone disease.

Clinical studies are ongoing with bortezomib in combination with pegylated liposomal doxorubicin, thalidomide, melphalan, and lenalidomide and have shown impressive disease control in refractory myeloma. In a randomized, phase III, multicenter, international study in patients with relapsed refractory myeloma, the combination of bortezomib (1.3 mg/m\(^2\) days 1, 4, 8, and 11) and pegylated liposomal doxorubicin (30 mg/m\(^2\) on day 4) was reported to be superior to bortezomib alone in terms of both overall response (50% vs 42%, respectively; \( P = .05 \)) and time to disease progression (9.3 months vs 6.5 months, respectively; \( P < .0001 \)). When bortezomib (1.0 or 1.3 mg/m\(^2\)) was administered with thalidomide (in doses ranging from 50 to 200 mg starting at cycle 2), 86% of patients with relapsed or refractory disease achieved a complete or partial response. A phase II study combining bortezomib with lenalidomide and dexamethasone has shown remarkable activity with minimal toxicity.

**Allogeneic stem cell transplantation**
For younger patients with resistant relapse or poor-prognosis disease (ie, deletion of chromosome 13), allogeneic transplantation may be an important option. The role of allogeneic transplant in myeloma should still be considered investigational. High-dose myeloablative therapy with allogeneic stem cell rescue has been abandoned in light of high transplant-related mortality. A nonmyeloablative regimen is ineffective in tumor cytoreduction and, consequently, is related to a high relapse rate. Thus, uniquely in multiple myeloma, high-dose melphalan and stem cell transplant is followed by a nonmyeloablative regimen and allogeneic stem cell transplantation. Two large, randomized trials from France and Italy that compared tandem autologous transplantation with autologous transplantation followed by allogeneic transplantation from matched sibling donors had different outcomes. French investigators noted no improvement in progression-free or overall survival when inclusion criteria were restricted to a high-risk group, whereas Italian investigators noted better event-free and overall survival when no such restriction for patient entry to the study were in place. In addition, chronic graft-versus-host disease inflicts considerable morbidity in excess of 50% of patients post-allograft.

**Supportive therapy**
Various supportive therapies may be beneficial in patients with multiple myeloma (Table 5).

**Chronic anemia**
The use of erythropoietic-stimulating agents (ESAs) in myeloma should be restricted to patients who are anemic due to concomitant myeloablative chemotherapy or moderate-to-severe renal failure. The combined use of ESA and immunomodulatory agents is associated with an increased incidence of venous thromboembolism. For additional information about the use of ESAs in patients with cancer visit [www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109375.htm](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109375.htm)

**Infection**
Serious infection with encapsulated organisms is encountered by patients with myeloma due to their inability to mount successful antibody production (and lack of opsonization). Prompt institution of antibiotics is therefore recommended in the face of systemic infection. Antibiotic prophylaxis is also
recommended whenever high-dose glucocorticoids are used for treatment. Patients with recurrent serious infections may benefit from monthly IV γ globulin. Shingles is not uncommon in these patients, and prophylaxis following transplantation and during bortezomib therapy is advised.

**Bone pain or imminent fracture**

Therapy with bisphosphonates, such as pamidronate, alendronate (Fosamax), or zoledronic acid (Zometa), may prevent or delay bone pain or recurrent or imminent pathologic fracture in patients with stage III disease and at least one bone lesion. Pamidronate administered over the long term (21 monthly treatments) to patients with stage III multiple myeloma with at least one lytic lesion reduces skeletal events and decreases the need for irradiation. Moreover, patients without lytic lesions also show a decrease in bone mineral density, and this decrease persists despite chemotherapy. These patients may also benefit from therapy with pamidronate. Several clinical and preclinical studies suggest that pamidronate may have an antimyeloma effect.

Zoledronic acid, a more potent bisphosphonate, has comparable efficacy and safety to pamidronate in preventing skeletal lesions. The ease of administration of a 4-mg dose, which reduces the infusion time to 15 minutes as compared with 2 hours for pamidronate, has led to approval of zoledronic acid by the FDA for prevention of bone-related complications in myeloma. Caution should be exercised with long-term use of bisphosphonates, as renal impairment and osteonecrosis of the jaw bones have been reported.

Percutaneous vertebroplasty provides pain relief that is not only rapid but sustained, and it also strengthens the vertebral bodies. Kyphoplasty is a safer procedure that involves insertion of a balloon followed by injection of polymethyl methacrylate, the principal component of bone cement, into the balloon. It is performed with the patient under local anesthesia. Transient worsening of pain and fever that may occur is responsive to nonsteroidal anti-inflammatory agents.

**Smoldering myeloma**

Smoldering, or asymptomatic, myeloma is characterized by the presence of monoclonal Ig > 3 g/dL and/or bone marrow plasmacytosis in excess of 10%. The diagnosis is often made by a chance finding of an elevated serum protein level during a screening examination.

**Laboratory features**

Features of low tumor mass are usually present, without renal disease, hypercalcemia, or lytic bone lesions (Table 2). Marrow plasma cytosis occurs in less than 30% of patients, and anemia, if present, is mild (hemoglobin value > 10.5 g/dL).

**Treatment**

Chemotherapy should be withheld until the patient becomes symptomatic. The role of bisphosphonates and thalidomide in this setting is under investigation, although a series of studies have suggested benefit from reducing the incidence of bone complications and increasing the time to progression with bisphosphonate use. An MRI finding of multifocal plasmacytomas or FDG-PET/CT findings of multifocal osseous lesions would be considered to be evidence of end-organ damage and would warrant initiation of systemic therapy.

**Prognostic factors** Smoldering myeloma generally progresses to multiple myeloma at the rate of 10% per year for the first 5 years, 3% per year for the next 5 years, and then 1% for the last 10 years. Risk factors for tumor progression include the serum level and isotype of the Ig, presence of Bence Jones proteinuria, excess free light chain in serum with abnormal free light-chain ratio, extent and pattern of bone marrow involvement, and reduction in uninvolved Ig.

**OTHER PLASMA CELL DYSCRASIAS**

Other plasma cell dyscrasias include MGUS, solitary plasmacytoma of bone (SPB), solitary extramedullary plasmacytoma, Waldenström's macroglobulinemia, amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, and heavy-chain diseases.

**MGUS**

MGUS occurs in 1% of normal individuals > 40 years old, and its frequency rises progressively with age.

**Laboratory features**

Common laboratory features of MGUS are listed in Table 2.

**Treatment**
Approximately 25% of patients with this disorder develop multiple myeloma, macroglobulinemia, or non-Hodgkin lymphoma over 20 years. The initial concentration of serum monoclonal protein > 1.5 g/dL, non-IgG-type paraprotein, and abnormal serum free light-chain ratio are significant predictors of disease progression at 20 years. The long period of stability supports annual monitoring with serum electrophoresis and blood counts and suggests that chemotherapy may be withheld until there is evidence of progression to myeloma.

**SPB**

Approximately 3% of patients with myeloma have SPB.

**Laboratory features**

All patients have either no myeloma protein or very low levels in serum or urine (Table 2). MRI may reveal abnormalities not detected by bone survey and may upstage patients to multiple myeloma. Persistence of monoclonal protein for more than 1 year after irradiation predicts early disease progression to multiple myeloma.

**Treatment**

Management of SPB consists of radiation therapy (at least 45 Gy). Multiple myeloma becomes evident in most patients over time, so only 20% of patients remain free of disease for more than 10 years. The median time for disease progression is approximately 2 to 3 years.

**Solitary extramedullary plasmacytoma**

In contrast to SPB, solitary extramedullary plasmacytoma is often truly localized and can be cured in up to 50% of patients with localized radiation therapy (45–50 Gy) and/or resection. Careful observation after treatment is nonetheless warranted.

**Waldenstrm's macroglobulinemia**

This uncommon disease is characterized by lymphoplasmacytic bone marrow and tissue infiltrate in addition to elevated IgM production. The mutation pattern analysis suggests that final transformation occurs in the postgerminal center IgM memory B cell. Corresponding with variation in cell morphology, there is variation in the immunophenotype. Mature plasma cells exhibit CD38 antigen; however, lymphoid cells are typically positive for CD19, CD20, and CD22. Waldenstrm's macroglobulinemia usually affects people in the fifth to seventh decades of life and can cause symptoms due to tumor infiltration (marrow, lymph nodes, and/or spleen), circulating IgM (hyperviscosity, cryoglobulinemia, and/or cold agglutinin hemolytic anemia), and tissue deposition of IgM (neuropathy, glomerular disease, and/or amyloidosis). Neuropathy may be due to the IgM antibody reacting with myelin-associated glycoprotein.

**Hyperviscosity syndrome**

With hyperviscosity syndrome, patients may have visual symptoms, dizziness, cardiopulmonary symptoms, decreased consciousness, and a bleeding diathesis. Therapy for hyperviscosity consists of plasmapheresis followed by chemotherapy to control the malignant proliferation. Patients with poor performance status and elderly patients who are unable to tolerate chemotherapy may be maintained with periodic plasmapheresis.

**Treatment**

Alkylating agents used in combination with steroids or purine analogs remain the mainstay of therapy. Alkylating agents alone or in combination with steroids effect a 50% reduction in paraprotein in about half of patients, and the median survival time is around 5 years. The purine analogs fludarabine (Fludara) and cladribine (Leustatin) elicit a more rapid response than other agents, with a response rate of more than 75% observed in a small series of patients. Preliminary results of a large, American multi-institution evaluation of fludarabine reported partial responses in only 33% of patients.

Purine analog therapy may result in significant myelosuppression in later cycles of therapy and prolonged immunosuppression with increased opportunistic infections. Purine analogs are effective salvage options in patients refractory to or relapsing following alkylator therapy. Patients refractory to one purine analog are rarely salvaged by a different purine analog. Patients with resistant relapse are less likely to benefit from purine analogs (response rate, 18%) and should be considered for more intensive intervention, including high-dose therapy.

**Other treatment options**

Rituximab (Rituxan), an anti-CD20 monoclonal antibody, is effective in Waldenstrm's
macroglobulinemia, because the CD20 antigen is usually present on the lymphoid cell component of macroglobulinemia. Preliminary results indicate that about 30% of previously treated patients (refractory or relapsing off therapy) may benefit from rituximab. Striking activity of thalidomide in multiple myeloma has prompted its use in Waldenström's macroglobulinemia. In a series of 20 patients receiving thalidomide, 25% achieved a 50% reduction in paraprotein. Higher doses of thalidomide were not well tolerated in an elderly cohort of patients. Interestingly, preliminary results of bortezomib-based therapy in relapsed Waldenström's macroglobulinemia have been promising. High-dose therapy with autologous bone marrow or blood stem cell rescue has been effective in achieving 50% reduction in paraprotein in almost all patients in small pilot trials.

Amyloidosis

Amyloidosis occurs in 10% of patients with multiple myeloma. This infiltrative process results from organ deposition of amyloid fibrils, which consist of the NH2 terminal amino acid residues of the variable portion of the light-chain Ig molecule. The abnormal protein is produced by clonal plasma cells.

Clinical features

These include the nephrotic syndrome, cardiomyopathy, hepatomegaly, neuropathy, macroglossia, carpal tunnel syndrome, and periorbital purpura.

Laboratory features

Serum and urine immunofixation studies show a monoclonal Ig in approximately 80% of patients. Measurement of serum free light chain may provide a marker to evaluate response to therapy. The light chain is more frequently of the λ than κ type. Diagnosis can be made by the presence of apple-green birefringence on polarized light examination of subcutaneous fat aspirates stained with Congo red. Elevated serum B-type natriuretic peptide levels may indicate cardiac involvement, which, in the majority of patients, may be confirmed with echocardiography.

Treatment of primary amyloidosis (AL; monoclonal protein–associated)

Survival of patients with amyloidosis is variable. Patients with congestive heart failure have a median survival of only 4 months. Oral MP extends the median survival to 17 months, as compared with 13 months in untreated patients. Complete hematologic response is rare; similarly, reversal of organ damage is uncommon.

In a large cohort of patients receiving high-dose melphalan with stem cell support, a complete hematologic response was observed in 47% of patients with at least 1 year of follow-up. However, the transplant-related mortality is high with high-dose therapy (14% to 37%). Complete hematologic response was associated with improved clinical response (improved organ function) and survival. Complete hematologic response in the absence of cardiac involvement predicted excellent outcome (1-year survival, 91%). Preliminary studies have also shown encouraging results with bortezomib as well as lenalidomide.

Patients with the overlap syndrome of myeloma and AL amyloidosis should be treated aggressively for myeloma; response can be seen in terms of both myeloma and resolution of amyloid symptoms.

POEMS syndrome

Clinical features and course

The POEMS syndrome is a rare plasma cell dyscrasia that presents with peripheral, usually sensorimotor, neuropathy; monoclonal gammopathy (IgA λ being more common); sclerotic bone lesions, noted in nearly all patients; and organomegaly, endocrinopathy, and skin changes. Other features include hyperpigmentation, hypertrichosis, thickened skin, papilledema, lymphadenopathy, peripheral edema, hepatomegaly, splenomegaly, and hypothyroidism. Diabetes mellitus is not part of this syndrome.

Compared with patients with symptomatic myeloma, individuals with POEMS syndrome are younger (median age, 51 years) and live longer (median, 8 years). The clinical course is commonly characterized by progressive neuropathy.

Treatment

Plasmapheresis does not appear to be of benefit in POEMS syndrome, and patients are often treated similarly to those with myeloma. Patients presenting with isolated sclerotic lesions may have substantial resolution of neuropathic symptoms after local therapy for plasmacytoma with surgery and/or radiotherapy. Autologous stem cell transplantation has been pursued in selected patients and has been associated with prolonged progression-free survival.
Heavy-chain diseases

Heavy-chain diseases are rare plasma cell dyscrasias characterized by the production of heavy-chain Ig molecules that lack light chains (IgG, IgA, IgM).

α Heavy-chain disease

This condition results from lymphocyte and plasma cell infiltration of the mesenteric nodes and small bowel and has features of malabsorption, such as diarrhea, weight loss, abdominal pain, edema, and nail clubbing. The heavy-chain molecule may be detected in serum, jejunal secretions, and urine. There is an association with infection with Campylobacter jejuni and α heavy-chain disease. Large proportions of patients can benefit from antibiotic therapy directed at this infection.

γ Heavy-chain disease

Patients with γ heavy-chain disease may present with fever, weakness, lymphadenopathy, hepatosplenomegaly, and involvement of Waldeyer's ring. Eosinophilia, leukopenia, and thrombocytopenia are common. Treatment with regimens similar to those used for non-Hodgkin lymphoma may be effective.

μ Heavy-chain disease

This condition is seen exclusively in patients with chronic lymphocytic leukemia (CLL). Vacuolated plasma cells are common in the marrow, and many patients have κ light chains in the urine. Therapy is similar to that used for CLL (see chapter 31).

References:

SUGGESTED READING

on multiple myeloma


on other plasma cell dyscrasias


Abbreviations in this chapter:
APEX = Assessment of Proteasome Inhibition for Extending Remissions; CIBMTR = Center for International Bone Marrow Transplant Registry; ECOG = Eastern Cooperative Oncology Group; EBMTR = European Bone Marrow Transplant Registry; FDA = US Food and Drug Administration; IFM = Intergroupe Francophone du Myélome; IMWG = International Myeloma Working Group; MRC = Medical Research Council; NCI = National Cancer Institute; SWOG = Southwest Oncology Group