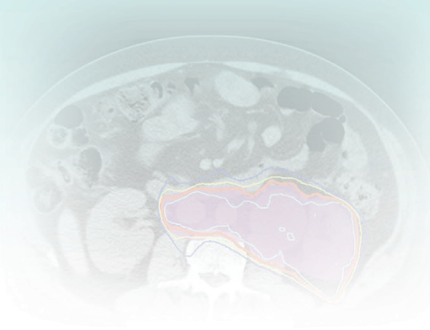
CHAPTER

78 Multiple Myeloma and Other Plasma Cell Neoplasms



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INCIDENCE AND EPIDEMIOLOGY

More than 24,000 new cases of multiple myeloma (MM) are diagnosed annually in the United States. MM accounts for 1.4% of all new cancers and 1.9% of cancer-related deaths. The rate in blacks is twice that in whites. Agricultural workers, woodworkers, and paper workers have a higher risk than other occupational groups.

ETIOLOGY AND BIOLOGIC CHARACTERISTICS

The etiology remains unknown. This hematologic malignant disease with mature plasma cell morphologic characteristics evolves from a cell late in B-cell development.

STAGING EVALUATION AND PROGNOSTIC FACTORS

The diagnosis of myeloma requires the presence of end-organ damage: anemia, elevated creatinine or calcium levels, and lytic bone lesions. Prognostic factors of most importance for MM are an increased β_2-microglobulin level and a decreased serum albumin level.

PRIMARY THERAPY AND RESULTS

Treatment of patients with symptomatic disease is indicated, excluding those with monoclonal gammopathic findings of undetermined significance or smoldering MM. The past decade has witnessed a dramatic improvement in the therapeutic options in MM. Several novel biologically targeted agents are in clinical use and have resulted in improved outcomes, including the proteasome inhibitors and immunomodulatory drugs. High-dose therapy with stem-cell transplantation remains a standard of care. A survival advantage of approximately 1 year has been shown for patients receiving high-dose therapy in two prospective randomized studies.

For solitary plasmacytoma of bone and extramedullary plasmacytoma, radiotherapy is the treatment of choice, with effective local control rates but high rates of progression to MM. Magnetic resonance imaging (MRI) may help to predict which patients are at higher risk of subsequent progression to MM.

TREATMENT OF PRIMARY REFRACTORY AND RELAPSING MYELOMA

Several promising drug therapy combinations are undergoing evaluation for refractory and relapsing myeloma. Localized radiotherapy is useful in palliation of painful or life-threatening disease.

Monoclonal gammopathies, also referred to as *paraproteinemias* or *dysproteinemias*, are a group of diseases characterized by the proliferation of a clone of plasma cells. The plasma cells produce an electrophoretically and immunologically homogeneous protein usually referred to as *monoclonal protein, M protein, M component*, or *paraprotein*. The progressive proliferation of plasma cells results in marrow replacement with a resulting normochromic or slightly macrocytic anemia. Direct infiltration of the overlying bony cortex by the malignant cells causes lytic bone disease, osteoporosis, and compression fractures of the spine. In addition, the production of a monoclonal light chain in the urine can result in a severe toxic response in renal tubules, with renal failure. Differentiation of monoclonal gammopathy of undetermined significance (MGUS) from MM and solitary plasmacytoma (SPB) is important to the selection of appropriate therapy and is discussed later in this chapter.

EPIDEMIOLOGY AND ETIOLOGY

An estimated 24,050 new cases of MM will occur in the United States in 2014, representing 1.4% of all new cases of cancer. MM accounts for 10% to 15% of all hematologic malignant diseases diagnosed in the United States, 20% of all deaths resulting from hematologic malignant diseases, and 1.4% of all cancer deaths. MM is an uncommon malignant disease in Pacific Rim countries.

The male-to-female ratio for the disease is 1.3:1. MM is a disease of older adults. The median age at diagnosis is 66 years; only 10% and 2% of patients are younger than 50 years and 40 years, respectively. The risk of developing MM is approximately 3.7-fold higher for persons with a first-degree relative with MM.

The average age of patients presenting with MM is approximately 63 years. In Olmsted County, Minnesota, the overall incidence of MM is 4.3 cases per 100,000 population per year.

Radiation has been linked to the pathogenesis of MM, but radiation exposure is found in only approximately 1% of patients. In the Hiroshima and Nagasaki tumor registries, there was no sign of an excess risk of MM.[1]

Data regarding the role of antigenic stimulation are conflicting. Epidemiologic studies in the United States have demonstrated associations between MM and agricultural workers.[2] An increasing trend for the incidence of lymphohematopoietic cancers has been associated with lifetime exposure to the chemical alachlor, a commonly used pesticide. The risk for MM gave a rate ratio of 5.66 in the highest exposure category.[3] Other occupational groups associated with the development of MM include miners, workers exposed to wood dust, and sheet metal workers.[4]

The etiology of MM remains unknown. Cytogenetic studies in MM demonstrate no consistent chromosome break point that identifies the majority of patients. Cytogenetic abnormalities, however, are less frequent in patients with MGUS, and an increase in frequency is seen as this condition evolves into MM untreated and MM relapsed. MM probably originates from a germinal center B cell of the lymph node. Receptors allow these cells to migrate from the lymph node to the bone marrow (BM).

Myeloma plasma cells express several adhesion molecules, including neural cell adhesion molecule (NCAM). Adhesion molecules are involved in homing of plasma cells to BM.

Although MM is a neoplasm of end-stage plasma cells, most investigators believe that myeloma stem cells exist as a self-renewing population derived from an earlier compartment. The identity of the cells responsible for the initiation and maintenance of MM remains unclear. Circulating B cells clonally related to MM plasma cells have been reported in some patients with myeloma. Data suggest that myeloma stem cells are CD138– B cells, whereas the terminally differentiated plasma cell is consistently CD138+, though this concept needs further validation. These CD138– B cells can replicate and differentiate into the malignant CD138+ plasma cells.[5] Overexpression of BCL-2 and BCL-6 proteins has been seen in clinical myeloma and myeloma cell lines.[6] Cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6, play an essential role in the biology of the malignancy as well as in mediating the bony manifestations of the disease. Both IL-6 and BCL-2 have been shown to prevent apoptosis, and IL-6 has been implicated as an essential growth factor in MM.[7]

PATHOLOGY AND MOLECULAR GENETICS

The morphology of the plasma cell in MM is relevant prognostically. Immature and plasmablastic plasma cells are associated with a poor prognosis. When 3% of the plasma cells in the BM are indistinguishable from lymphoblasts, this has been defined as *plasmablastic myeloma* and is associated with a higher prevalence of renal insufficiency and bone disease. Other prognostic features seen on evaluation of the BM biopsy specimen include marked dysplasia, number of mitoses per high-power field, and packing of the BM by tumor.

MM is distinct in that the BM is involved in virtually all patients (Figure 78-1), yet the peripheral blood shows large numbers of circulating cells in only a few patients. Adhesion molecules mediate both homotypical and heterotypical adhesion of tumor cells to either extracellular matrix (ECM) proteins or BM stromal cells. They play a critical role in disease progression. After class switching in the lymph node, adhesion molecules (e.g., CD44, VLA-4, VLA-5, LFA-1, CD56, syndecan-1, and MPC-1) mediate homing of MM cells to the BM stromal cells. Syndecan-1 is a multifunctional regulator of tumor cell growth and survival as well as of bone cell differentiation, and elevated serum syndecan-1 correlates with increased tumor cell mass, decreased metalloproteinase-9 activity, and poor prognosis.[8] Syndecan-1 is shed from the surface of most MM cells, induces apoptosis and can inhibit the growth of MM cells; it also mediates decreased osteoclast and increased osteoblast differentiation.[8] Novel agents, including thalidomide, and derivatives (IMiDs), including lenalidomide, as well as the proteasome inhibitor bortezomib can target both the tumor cell and its BM microenvironment, thereby overcoming cell adhesion-mediated (CAM) conventional drug resistance.[9,10] *TP53* mutations are associated with more advanced myelomas and are related to the terminal phases of the disease.[11] Mutations of *RAS* are more prevalent in MM than in other lymphoid malignant diseases. In a study using genomic DNA in 128 patients, *RAS* mutations were far more common in patients with aggressive plasma cell leukemias (30%) than in MM patients (9%). The *RAS* mutations appear to represent a late molecular lesion in the process of myeloma evolution. When levels of *RAS* were studied in 160 patients with newly diagnosed MM, the median survival rate for patients with mutations of N-*RAS* was no different from that of patients with no *RAS* mutations. However, patients with K-*RAS* mutations had significantly higher tumor burdens at diagnosis and a median survival time of 2 years versus 3.7 years for those who did not have K-*RAS* mutations. The *RAS* mutations appear to have an independent impact on the median survival rate of patients with MM.[12]

IgH rearrangements can be found in 75% of patients. Dysregulation of cyclin D_1 can be detected in 30% of MM tumors. Cell lines that overexpress cyclin D_1 have a translocation detectable into a gamma switch region that suggests an error in VDJ recombination. V_H analysis of the clonal cells in MGUS showed much lower mutation frequencies than in MM. The clonogenic cell in MM likely originates from a preswitched but somatically mutated B cell. Genetic studies have demonstrated that the progression of MM from plateau phase to relapse does not involve a new B-cell clone, and progression beyond the plateau phase is not the result of clonal succession.[13] Advances using molecular probes for fluorescence in situ hybridization (FISH) have demonstrated aneuploid chromosomes where conventional cytogenetics are normal. Chromosome 13 abnormalities on metaphase cytogenetics have been associated with an unfavorable prognosis in patients with myeloma. The translocation t(11;14) results in up-regulation of cyclin D_1 and is the most common translocation detected in patients with MM. Sixteen percent of patients carry the t(11;14) and have better survival and response to therapy rates.[14] Immunoglobulin heavy-chain translocations are seen in 60% of patients, and these translocations are more likely to be nonhyperdiploid. Patients with light-chain myeloma never display a functional immunoglobulin heavy-chain recombination. Most patients with light-chain myeloma have one immunoglobulin heavy-chain allele with a germline configuration. The second allele is usually involved in an illegitimate recombination. Light-chain myeloma may be the result of the absence of legitimate immunoglobulin heavy-chain rearrangement at the DNA level.[15]

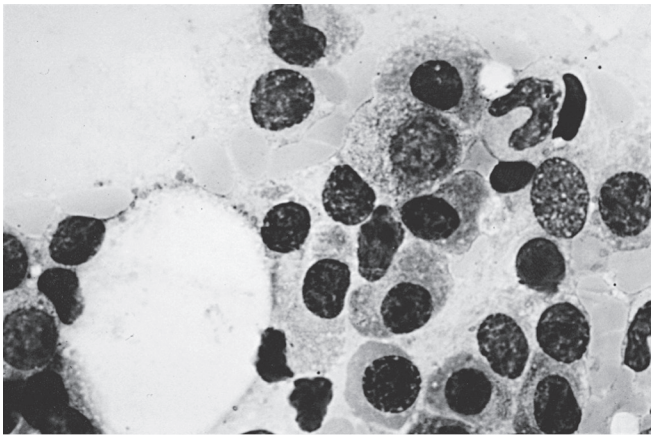

Figure 78-1 Bone marrow diagnostic for multiple myeloma. (Wright stain; original magnification ×1000.)

CLINICAL MANIFESTATIONS AND PATIENT EVALUATION

Multiple Myeloma and Monoclonal Gammopathy of Undetermined Significance

The key to early detection of MM is recognizing the associated clinical syndromes and presentations and permitting appropriate diagnostic tests to be performed. The clinician must order electrophoresis of serum and urine for all patients who present with normochromic normocytic or slightly macrocytic anemia. Electrophoresis of serum and urine can often obviate needless diagnostic investigations for gastrointestinal tract blood loss or other invasive techniques. In a patient who has

Figure 78-2 Advanced compression fractures of multiple myeloma. Note the lack of features specific for malignancy.

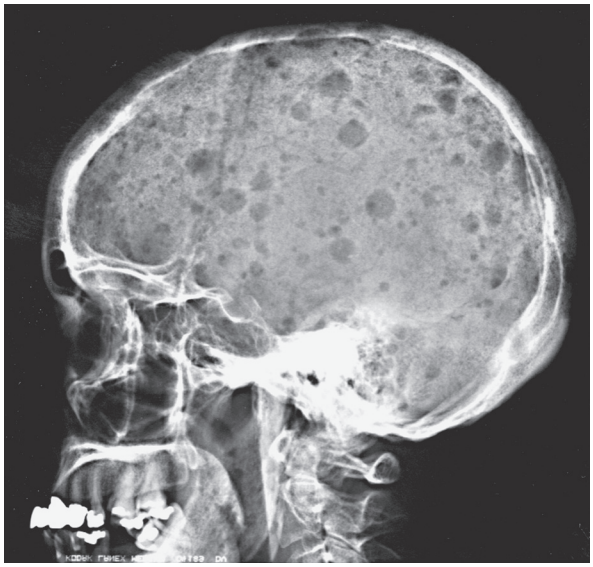

Figure 78-3 Calvarial radiograph from a patient with multiple myeloma.

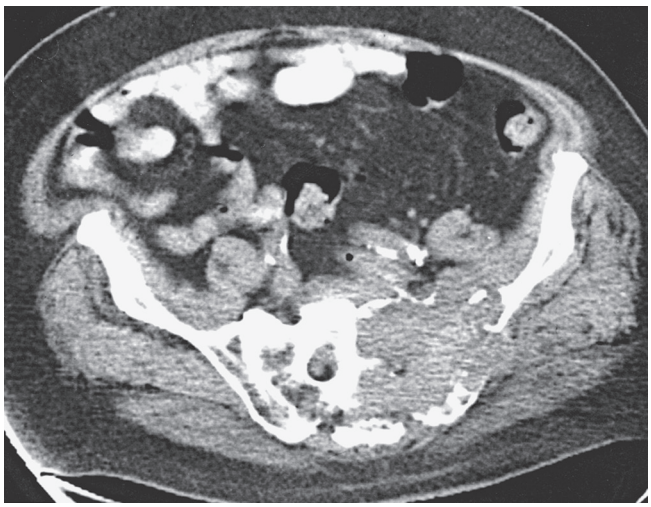

Figure 78-4 Diagnostic computed tomographic scan of pelvic plasmacytoma. Plain radiographs revealed only rarefaction and were not diagnostic.

any degree of unexplained renal insufficiency (i.e., a nonhypertensive, nondiabetic patient), urine immunoelectrophoresis often leads to recognition of myeloma cast nephropathy.

Bone involvement is frequent in patients with myeloma and bone pain is a common problem. Radiographs of the spine in patients with MM frequently show osteoporosis and compression fractures. It is virtually impossible to distinguish the compression fractures associated with MM from those seen in patients with senile osteoporosis (Figure 78-2). Spine radiographs poorly demonstrate the small lytic lesions frequently responsible for collapse of these vertebrae. All patients with back or rib pain, even with no malignant features on radiographs, should have electrophoresis of serum and urine. If a monoclonal protein is found, radiographs of the entire skeleton often demonstrate lytic lesions in the calvaria, pelvis, and long bones of the humerus and femur (Figure 78-3).

Assessment of bone disease initially requires a radiographic bone survey. Because the lesions of MM are primarily lytic, with little evidence of bony repair, radionuclide bone scans tend to be an inferior approach. In difficult cases in which osteoporosis and monoclonal gammopathy are found with no other changes, computed tomography (CT) scan or MRI of the spine and pelvis can be valuable in detecting clear-cut evidence of neoplasia (Figure 78-4). Positron emission tomography (PET) may be useful in MM because the lytic lesions are PET avid. When 66 patients were studied with PET and compared with CT and MRI, negative PET findings reliably predicted stable MGUS.[16] All patients with active myeloma had focal or diffusely positive scans, four of whom had negative full radiographic bone surveys. Extramedullary uptake was detected by PET in 23% of relapsing patients. PET also tracks response, showing a decline in lesion metabolic activity with successful intervention. It is more sensitive than other imaging techniques, and it can find additional lesions in a third of patients, which affected therapeutic decision making for a quarter of these patients.[17]

Failure to perform electrophoresis studies in patients presenting with back pain or osteoporosis can delay a diagnosis of MM. The need for screening electrophoresis cannot be overemphasized. The most common reason for a delayed diagnosis of MM is the simple finding that MM was not included in the differential diagnosis.

A second clinical problem is distinguishing MGUS from overt MM. In MGUS, the patient is expected to be asymptomatic, without evidence of anemia, hypercalcemia, bone involvement on skeletal survey, or renal insufficiency. In the absence of symptoms and with a low monoclonal protein value, regular monitoring of the level of the monoclonal protein should suffice. Patients with monoclonal gammopathies, however, should be monitored indefinitely because the risk for transformation to a malignant plasma-proliferative process is approximately 1% per year. The risk for transformation is predicted by the initial size of the M protein peak. Patients

with low monoclonal protein levels (≤0.5 g/dL) had a 6% risk for developing MM at 10 years compared with an 11% risk at 10 years for those with a 1.5-g/dL peak and a 24% risk at 10 years for those with a 2.5-g/dL peak.[18]

The frequency of monitoring patients with MGUS depends on risk factors identified at initial evaluation. Although there are no findings at diagnosis of MGUS that reliably distinguish patients who will remain stable from those who will progress to MM, the size and type of the M protein at diagnosis are predictive factors for progression of MGUS to myeloma or related malignant disease. MGUS is associated with a low risk of progression when the M protein level is less than 1.5 g/dL. Patients with IgM or IgA monoclonal protein had a significantly increased risk of progression to disease, as compared with patients having an IgG monoclonal protein. Presence of an abnormal (monoclonal) kappa/lambda free light-chain ratio in the serum is also associated with a significantly higher risk of disease progression.

Staging of Multiple Myeloma

Classification of patients with MM by stage is important. Comparison of outcomes in single-arm studies of MM depends on patient selection and case mix. Therefore, ensuring that patients have comparable severity of disease is important when comparing the outcomes of various studies. In addition, stage may be useful in selecting patients with unfavorable outcomes for more intensive therapies. Conversely, patients who are at a low stage and whose prognosis is good may be candidates for less intensive therapies and may achieve outcomes similar to those of aggressively treated patients.

The most widely accepted classification is the International Myeloma Working Group staging system, where stage III myeloma is a β_2-microglobulin level higher than 5.5 μg/mL. Stage I includes patients with a β_2-microglobulin level that is less than 3.5 μg/mL and a serum albumin level that is less than 3.5 g/dL, and stage II includes all patients who do not fit stage I or stage III (Table 78-1).

The older staging system in clinical use is that of Durie and Salmon (Table 78-2). One problem with the Durie-Salmon staging system is that the criteria for stage I MM in this scheme are also consistent with smoldering MM and indolent MM, which do not require any form of therapy. In most clinical therapy studies, no more than 10% of patients have stage I disease, and many studies exclude patients with stage I from participation. The second difficulty is the subjective nature of interpretation of advanced lytic lesions to distinguish stage II from stage III. No specific well-defined criteria exist to ensure that all institutions use the same definition of advanced MM.

Response is generally assessed by the reduction in monoclonal protein; a reduction of 25% to 50% is considered a minor response and 50% to 99% an objective response. Complete eradication of the monoclonal protein in the serum and in the urine with less than 5% plasma cells in the BM is considered a complete response. Patients who either did not have a BM test performed or whose monoclonal protein was no longer visible but detectable by immunofixation are considered to have a near-complete response. In recipients of autologous transplants, a complete response predicts improved outcome after transplantation.[19]

TABLE 78-1 International Myeloma Working Group Staging System

Stage	Criteria
I	β_2-microglobulin <3.5 μg/mL and albumin ≥3.5 g/dL
II	β_2-microglobulin <3. μg/mL and albumin <3.5 g/dL or β_2-microglobulin = 3.5-5.5 μg/mL
III	β_2-microglobulin ≥5.5 μg/mL

THERAPY FOR MULTIPLE MYELOMA

The treatment of MM is reserved for patients who are symptomatic. There are ongoing studies to assess impact of treatment in patients with high risk smoldering myeloma. Generally, outside a clinical trial, observation is currently recommended for patients with smoldering myeloma.

Most patients with MM have symptomatic disease at diagnosis and require systemic therapy. Specific indications for treatment include decreasing concentration of hemoglobin, increasing concentration of calcium and creatinine, lytic bone lesions, and extramedullary plasmacytoma.

Patients undergoing therapy for MM should have clinical and laboratory assessment to ensure both safety and efficacy of treatment (Table 78-3). Before each course of treatment, a complete blood count, including differential and platelets, should be done. Serum chemistries should be measured at

TABLE 78-2 Durie-Salmon Staging System of Multiple Myeloma

Stage	Criteria
I	All of these required: hemoglobin >10 g/dL, Ca^{2+} <10.5 mg/dL, IgG <5 g/dL or IgA <3 g/dL and light-chain loss <4 g/dL No lytic bone lesions
II	Not fitting stage I or III
III	Any one of the following: hemoglobin <8.5 g/dL, Ca^{2+} >12 mg/dL, IgG >7 g/dL, IgA >5 g/dL, or light-chain loss >12 g/dL Advanced lytic lesions
IIIA	Creatinine <2 mg/dL
IIIB	Creatinine ≥2 mg/dL

TABLE 78-3 Required Testing to Evaluate Multiple Myeloma

Category	Test
Blood	Complete blood cell count Creatinine Calcium Sodium, potassium Uric acid Albumin Alkaline phosphatase Aspartate aminotransferase Serum protein electrophoresis with immunofixation Serum free light-chain assay β_2-microglobulin Lactate dehydrogenase C-reactive protein
Urine	Urine protein electrophoresis Urine immunofixation Creatinine clearance
Radiography	Skeletal survey
Miscellaneous	Electrocardiogram Bone marrow aspirate and biopsy

least every 3 months or more often if clinically indicated. Concomitantly, monoclonal protein in the serum should be measured by immunoelectrophoresis or, preferably, using more sensitive immunofixation techniques and a serum free light-chain assay must be done in patients with light-chain disease. A skeletal survey should be done annually, with BM examination reserved for diagnosis and time of subsequent change in clinical status, in monoclonal Ig, or in hemogram. A BM examination is typically done at diagnosis and subsequently at the time of change in clinical status (i.e., for assessment of response or at time of relapse).

Treatment and Emerging Novel Therapies

In patients who are candidates for hematopoietic cell transplantation (HCT), induction chemotherapy is administered for 2 to 4 months before stem-cell collection to reduce the number of tumor cells in the BM and peripheral blood, lessen symptoms, and mitigate end-organ damage.

There has been a shift in the treatment paradigm in MM toward moving away from conventional chemotherapy and incorporating the use of novel agents. Thalidomide was used as a sedative and antiemetic in the 1950s, when it was withdrawn from the market as a result of teratogenicity. Its exact mechanism of action is unknown, but its antiangiogenic properties are thought to inhibit the growth of myeloma. Thalidomide also alters the adhesion of myeloma cells to the BM stroma. Several trials using thalidomide in the management of relapsed MM have shown response rates from 30% to 45%.[20] There is no clear relationship between dose and response. Although doses of up to 800 mg have been used, 50 mg to 200 mg is the typical dose for long-term management. The side effects of thalidomide are significant and, when combined with dexamethasone, deep vein thrombosis occurs in 16% and grade III or IV toxicities in 44% of patients.

Lenalidomide was developed as a thalidomide analog, using the structural backbone of thalidomide but with the elimination of a carbonyl group and the addition of an amine, originally to more effectively inhibit TNF-α. Several other potential mechanisms for the anti-MM effect of lenalidomide have been identified. Lenalidomide was noted to have a better side effect profile, with decreased peripheral neuropathy, somnolence, and gastrointestinal toxicity compared with thalidomide, but with greater myelosuppression. The favorable side effect profile and efficacy of lenalidomide was confirmed in two large, randomized, multicenter, double-blind, placebo-controlled studies in patients with relapsed or refractory myeloma—the MM-009 North American trial and the MM-010 European/Israeli/Australian trial.[21,22] In both studies, patients were randomized to receive 25 mg of oral lenalidomide or placebo on days 1 to 21 of a 28-day cycle. All patients received dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles and subsequently, after the fourth cycle, only on days 1 to 4. The median time to progression was significantly longer in the lenalidomide/dexamethasone combination (MM-009: 11.1 months; MM-010: 11.3 months) compared with placebo/dexamethasone (4.7 months in both trials). Similar superiority was seen for the lenalidomide/dexamethasone combination in terms of overall response (OR) rate (MM-009: 61%; MM-010: 60.2%) compared with placebo/dexamethasone (MM-009: 19.9%; MM-010: 24%).

In a Phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG E4A03), 445 previously untreated patients with MM were randomly assigned to lenalidomide plus "standard" high-dose dexamethasone (40 mg/day by mouth on days 1 to 4, 9 to 12, and 17 to 20 of each cycle) versus lenalidomide plus lower-dose dexamethasone (40 mg by mouth on days 1, 8, 15, and 22 of each 28-day cycle).[23] The trial was stopped prematurely by the data safety monitoring committee because mortality was increased in the high-dose dexamethasone arm.

Pomalidomide, a new immunomodulatory agent, has demonstrated significant anti-MM activity in patients who have disease refractory to thalidomide, lenalidomide, or bortezomib. Pomalidomide in combination with dexamethasone has demonstrated response ~35% in patients with prior treatment with lenalidomide, thalidomide, and bortezomib.[24,25]

Prophylaxis against clotting with aspirin, Coumadin, or subcutaneous heparin is needed when patients are treated with lenalidomide or pomalidomide therapy.

Bortezomib represents a novel class of anticancer compounds, the proteasome inhibitors. These drugs induce cell death by blocking degradation of apoptotic molecules that are normally catabolized via proteasome proteolysis. They inhibit nuclear factor kappa B (NFκB) activation by stopping the cleavage of its bound suppressor. Increased NFκB activity has been described in myeloma cells, and proteasome inhibitors seem to overcome chemotherapy resistance. A Phase III study of bortezomib with dexamethasone suggested that the time to progression was prolonged in the bortezomib group. Bortezomib produces a response in approximately one third of patients with relapsed MM; its primary toxic effects are thrombocytopenia and peripheral neuropathy.[26]

The bench to bedside translation of bortezomib and approval by the U.S. Food and Drug Administration (FDA) were also rapid. NFκB was identified as a target in MM because it conferred drug resistance, modulated adhesion molecule expression on MM cells and BM stromal cells, and modulated constitutive and MM binding-induced transcription and secretion of cytokines. Phase I trials showed tolerability and early evidence of anti-MM activity. The Phase II SUMMIT trial demonstrated responses in relapsed refractory MM, including complete responses, prolongation of time to progression and survival, and associated clinical benefit.[27] The Assessment of Proteosome Inhibition for Extending Remissions (APEX) trial, which compared dexamethasone versus bortezomib therapy of relapsed MM, was unblinded because of a statistically significant prolongation in time to progression in the bortezomib-treated cohort, forming the basis for its FDA approval extending to relapsed MM.[26] With follow-up, time to progression and overall survival rates are significantly improved with bortezomib and neurologic complications manageable.

Carfilzomib is a novel irreversible proteasome inhibitor of the epoxyketone class that is selective for the chymo-trypsin-like protease, with less affinity for other proteasome proteases. In the open-label, single-arm Phase II PX-171-003-A1 study, patients received carfilzomib 20 mg/m^2 intravenously twice weekly for 3 out of 4 weeks in cycle 1, then 27 mg/m^2 for up to 12 cycles with low-dose dexamethasone as premedication. Patients had a median of five prior lines of therapy and 80% were refractory to or intolerant of both bortezomib and lenalidomide. The overall response rate was 23% with median duration of response of 7.8 months and a median overall survival of 15.6 months. Common adverse events included fatigue (49%), anemia (46%), nausea (45%), and thrombocytopenia (39%). Twelve percent of patients experienced peripheral neuropathy, primarily grades 1 to 2.[28]

In the PX-171-004 study, carfilzomib with low-dose dexamethasone premedication was given to patients with MM who were bortezomib-naïve. Patients in cohort 1 received IV carfilzomib 20 mg/m^2 for all treatment cycles, whereas those in cohort 2 received 20 mg/m^2 in cycle 1 and 27 mg/m^2 in subsequent cycles. The clinical benefit (minimal response or better) was 59% and 64% in cohorts 1 and 2, respectively. Median duration of response was 13 months and not reached in the respective cohorts, and median time to progression was

8 months and not reached, respectively. The most common treatment-related adverse events were fatigue (62%) and nausea (48%). There was a relatively low incidence of peripheral neuropathy at 17% and other nonhematologic toxicity proved manageable.[29]

The combination of bortezomib, lenalidomide, and dexamethasone has been studied in the relapsed/refractory and upfront setting. In the upfront setting, 66 patients received eight 3-week cycles of bortezomib 1 mg/m^2 to 1.3 mg/m^2 (days 1, 4, 8, and 11), lenalidomide 15 mg to 25 mg (days 1 to 14), and dexamethasone 40 mg or 20 mg (days 1, 2, 4, 5, 8, 9, 11, and 12). Responding patients proceeded to maintenance or transplant. Phase II dosing was determined to be bortezomib 1.3 mg/m^2, lenalidomide 25 mg, and dexamethasone 20 mg. The rate of partial response or better was 100% in both the Phase II population and overall, with 74% and 67% achieving a very good partial response or better. Adverse cytogenetics had no effect on the rate of response or progression-free survival (PFS).[30] The combination of lenalidomide, carfilzomib, and dexamethasone has demonstrated similar impressive results.[31]

The combination of pomalidomide, carfilzomib, and dexamethasone has been shown to have encouraging results even in patients with high-risk features in a preliminary study in patients with relapsed/refractory myeloma.[32]

Monoclonal antibodies [MoAbs] are as an important modality in the treatment of myeloma. Examples include anti-CS1 MoAb elotuzumab, anti-CD 38 MoAbs (daratumumab, SAR 650984) and anti-CD 138 antibody conjugate BT062 comprised of the anti-CD138 chimerized MAb and the cytotoxic agent DM4,[33-35] which are being evaluated in clinical trials presently.

Stem-Cell Transplantation

The use of alkylating agents (melphalan, cyclophosphamide, busulfan) in a higher-than-conventional dose followed by infusion of autologous stem cells as part of management is considered the standard of care. In one prospective randomized study, the probability of event-free survival for 5 years was 28% in the transplant group and 10% in the conventional-dose group.[36] The estimated rate of survival for 5 years was 52% in the high-dose group and 12% in the conventional-dose group (p = 0.03). The U. K. Medical Research Council, in a prospective randomized study, demonstrated a higher rate of complete response, 44%, versus 8% with conventional therapy, and an improved overall survival time of 54.1 months versus 42.3 months.[37] Patients with sensitive disease and who are less heavily pretreated have the most favorable outcomes.

In 162 patients who had allogeneic BMT for MM, the European Group for Blood and Marrow Transplantation (EBMT) reported a 32% survival rate at 4 years and a 28% rate at 7 years.[38] In the 72 patients (44%) who achieved complete remission after BMT, the overall PFS rate was 34% at 6 years. Only 9 patients, however, remained in complete remission more than 4 years after allogeneic BMT. With allogeneic BMT, some of the decreased survival time can be attributed to peritransplantation mortality, approaching 40% in some series, because of graft-versus-host disease and other complications of the procedure itself.

Because of these difficulties with allogeneic BMT, autologous peripheral blood stem-cell transplantation has become the more common procedure in the treatment of untreated, refractory, or recurrent MM. Applicability to older patients (upper age limit of 75 years in many centers) without the need for a matched donor and with less risk for transplant-related mortality (<3% in larger centers) has made this procedure accessible to more patients with MM. The disadvantages of autologous BMT in this BM malignant disease include the difficulty of removing tumor cells from the transplanted peripheral blood or marrow and the lack of a potential graft-versus-myeloma effect.

In a prospective randomized study, sequential tandem autologous transplantation demonstrated superior survival rates compared with single stem-cell transplantation. Drawbacks of this study included conditioning that does not conform to current standards and the fact that the single-transplant group achieved a median survival time of only 48 months, which is shorter than survival times in many other reported studies.[39] The second transplantation is normally completed within 6 months of the first.

The benefit of high-dose chemotherapy and autologous stem-cell transplantation in the era of novel agents is the focus of ongoing studies.

The principal characteristics that determine eligibility for HCT are performance status or the presence and severity of certain comorbid conditions. Among patients with symptomatic standard-risk MM who are not candidates for autologous HCT, we recommend a regimen consisting of lenalidomide plus low-dose dexamethasone, Velcade (bortezomib), melphalan, and prednisone (VMP) or bortezomib plus low-dose dexamethasone. In a prospective Phase III randomized trial comparing VMP with melphalan and prednisone (MP) in the treatment of 682 older adults (median age 71 years) with newly diagnosed MM at a median follow-up of 16.3 months, patients treated with VMP had a significantly longer median time to progression (24 months versus 17 months), and higher rates of overall survival (87% versus 78%) when compared with those treated with MP.[40] Combined with prior data, these results led to the approval of VMP by the FDA for the initial treatment of MM.

In a Phase III trial comparing the efficacy and safety of Revlimid and dexamethasone to that of melphalan plus prednisone and thalidomide in patients with newly diagnosed MM who were 65 years and older (median age of 73 years) or not eligible for stem-cell transplantation, patients were divided into one of three treatment groups, receiving either Revlimid plus dexamethasone (Rd) until disease progression, Rd for 72 weeks, or melphalan plus prednisone and thalidomide (MPT) for 72 weeks. The results showed that more patients responded to continuous treatment with Revlimid (75%) than 72 weeks of RD (73%) or MPT (62%). The median PFS was significantly longer for those who received continuous Rd (26 months) than for those who received Rd for 72 weeks (21 months) and those who received MPT (21 months). The differences in PFS became apparent at the 72-week mark when two of the groups discontinued treatment. The 4-year overall survival was longest for those who received continuous Rd (59%), compared to those who received Rd for 72 weeks (56%) and those who received MPT (51%). The difference was significant for continuous Rd compared to MPT.[41]

Maintenance Therapy

Novel therapies are now being evaluated to prolong PFS rates. For example, the 3-year median and overall PFS times were prolonged by the use of thalidomide following transplantation. Thalidomide with or without prednisone has been evaluated as maintenance. Because lenalidomide is an oral drug with fewer side effects, it has undergone evaluation as maintenance treatment. In a Phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed MM, the PFS rate was significantly improved in patients who received MPR followed by lenalidomide maintenance

compared with those who received MP followed by placebo maintenance.[42] In a Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem-cell transplant (CALGB 100104) maintenance therapy with lenalidomide, when compared to placebo, prolonged time to disease progression. The median time to progression was 46 months in the lenalidomide group and 27 months in the placebo group ($p < 0.001$).[43]

Supportive Treatment

Newer supportive modalities are useful in the management of patients with MM. Although chemotherapy can destroy the malignant clone and may prevent progression of bony disease, it does not lead to remineralization or recalcification of previously involved bone. Monthly infusions of pamidronate or zoledronic acid for 9 consecutive months reduced the proportion of patients who had any skeletal events from 41% to 24%.[44] Patients who received pamidronate had significant decreases in bone pain and an improved quality of life. Pamidronate or zoledronic acid has a significant palliative effect in patients with bone pain secondary to metastasis. Bisphosphonates act by inhibiting bone resorption. They have a major effect on osteoclasts and reduce bone-resorbing cytokine production. Zoledronic acid is 100 times more potent than the bisphosphonate most commonly administered orally, alendronate. These agents reduce the frequency of skeletal-related events, including the need for irradiation for bone pain, pathologic fracture, and spinal cord compression. The toxic effects of bisphosphonates include an increase in the serum creatinine level, proteinuria, and osteonecrosis of the jaw. Vertebroplasty is high-pressure injection of low-viscosity material into the vertebral body, designed to stabilize painful vertebral compression fractures. It can be done on an outpatient basis by an interventional radiologist. Its risks include leak of the material and encroachment on a nerve root.

Solitary Plasmacytoma

Solitary plasmacytoma, which accounts for 5% to 10% of all plasma cell dyscrasias, is characterized by the presence of a plasmacytoma in the absence of multiple osteolytic lesions or other features of MM.[45] Approximately two thirds of the cases are solitary plasmacytomas of the bone, which most commonly involve the axial skeleton, while the remaining one third are extramedullary plasmacytomas, most frequently presenting in the upper aerodigestive tract. Progression to MM is more likely to occur in plasmacytoma of the bone than in extramedullary plasmacytoma.[46] The 5-year and 10-year rates of progression to MM in patients with solitary plasmacytoma of the bone are 30% to 50% and 70% to 90%, respectively, whereas around 10% to 35% of patients with extramedullary plasmacytoma eventually progress to MM.[47,48]

Definitive radiation therapy is considered standard therapy for patients with solitary plasmacytoma. Retrospective series using doses ranging from 35 Gy to 60 Gy showed a more than 80% local control rate. In the largest series to date reported by the European Multicenter Rare Cancer Network, which included 258 patients with solitary plasmacytoma (206 with solitary plasmacytoma of the bone and 52 with extramedullary plasmacytoma), the median dose of radiation therapy was 40 Gy (range, 20 Gy to 66 Gy).[49] At a median follow-up time of 56 months, 14% of patients developed a local recurrence (median, 20 months). The 10-year probability of progression to MM was 72% for solitary plasmacytoma of the bone and 36% for extramedullary plasmacytoma.

Several studies have evaluated optimal radiation doses for solitary plasmacytoma,[47,49-55] although most have failed to show a significant dose-response relationship. In the study by the European Multicenter Rare Cancer Network,[49] after adjusting the radiation dose to a biologically equivalent dose (BED) of 2 Gy per fraction, no dose-response relationship was observed for doses of more than 30 Gy. Of the 244 patients treated with radiation therapy, 2 (6%) of 32 patients treated with 30 Gy or less developed local failure compared with 27 (13%) of 212 patients treated with more than 30 Gy. When limiting the analysis to tumors of 4 cm or larger, there continues to be a lack of a significant dose-response relationship beyond 30 Gy. Other smaller series also failed to show significant differences in local control rates with doses of less than 30 Gy versus higher doses.[47,51,54] A meaningful evaluation of optimal radiation dose may be limited by the retrospective nature and the small patient numbers in the available studies. Suh et al reported on radiation treatment outcome of 38 patients with solitary plasmacytoma and found that radiotherapy doses of >40 Gy was associated with a significantly higher local control rate (10-year local control of 100% versus 60%, $p = 0.04$).[56] One study from France on 17 patients with extramedullary plasmacytoma of the head and neck region,[52] showed that a dose of >45 Gy to the target volume is associated with an improved local control rate (5-year local control of 100% versus 50%, $p = 0.034$). In a study from Turkey that included 80 patients with solitary plasmacytoma,[50] on multivariable analysis, doses of 50 Gy or less were associated with a significantly lower PFS rate (hazard ratio [HR], 2.3; $p = 0.04$). Although data supporting the use of higher doses are limited, most centers recommend doses of 45 Gy to 50 Gy in 1.8-Gy to 2-Gy daily fractions as definitive treatment for patients with solitary plasmacytoma.

The optimal radiation treatment volume has not been specifically addressed for solitary plasmacytoma. However, it is generally acceptable to include the gross disease plus a margin of 2 cm. Patients with extramedullary plasmacytoma, especially of the head and neck region, may benefit from treatment with intensity-modulated radiation therapy (IMRT) techniques to limit doses to normal structures and to preserve the quality of life.[47] For these patients, most series also included clinically uninvolved regional nodes in the treatment volume. In the European Multicenter Rare Cancer Network study, however, which also included 52 patients with extramedullary plasmacytoma,[49] the planning radiation treatment volume was limited to the radiographically visible gross tumor volume plus a margin; no attempt was made to cover regional lymph nodes. At a median follow-up time of 54 months, no regional nodal relapses were observed.

Investigators have explored factors predicting for local recurrence and progression to MM in patients with solitary plasmacytoma. Findings on the impact of tumor size on local control rates have been conflicting. Tsang et al showed that the 8-year local control rate was 100% for tumors of less than 5 cm as compared with 38% for tumors of 5 cm or more in diameter ($p < 0.01$).[54] Dagan et al reported local control rates of 100% and 79%, respectively, for tumors of 5 cm or less versus tumors larger than 5 cm, although the difference did not reach statistical significance ($p = 0.09$).[47] Others, however, have failed to show a significant relationship between tumor size and local control rates.[53,55,57,58]

The anatomic location of the tumor can also influence local control rates. Knobel et al demonstrated a trend to higher 10-year local control rates for presentation in vertebral bodies versus other sites (89% versus 78%; $p = 0.07$).[53] The previously described Turkish study showed that surgical resection before radiation therapy is associated with an improved PFS rate. Similarly, a study from Japan on 67 patients with solitary extramedullary plasmacytoma of the head and neck found radiotherapy combined with surgery to be an independent

prognostic factor for overall survival.[58] However, in a study by Ozsahin et al, complete or partial resection prior to radiation therapy had no impact on local control rates.[49] The same study showed that surgery alone for solitary plasmacytoma is clearly inadequate: 7 of 9 patients (78%) treated with surgery without radiation therapy relapsed locally, as compared with 29 of 248 patients (12%) who received radiation therapy. Other factors that have been associated with inferior prognosis include older age at diagnosis[49,50,53] and persistence of myeloma protein for more than 1 year after radiotherapy.[59,60]

Radiation Therapy as Palliation in Multiple Myeloma

Radiation therapy represents an effective form of palliation for patients with MM with symptomatic local involvement.[61,62] The main indications for palliative radiation therapy include bone pain with or without pathologic fractures, neurologic compromise including cord compression, impending cord compression, nerve root compression, or cranial nerve deficits. Patients with impending fractures of weight-bearing bones should first be evaluated by an orthopedic surgeon for consideration of surgical stabilization. Patients with compression fractures of vertebral bodies may also benefit from vertebroplasties or kyphoplasties before radiation therapy.[62-65] For cases of cord compression with associated acute neurologic symptoms, prompt neurosurgical intervention may improve the chance of neurologic recovery, as has been demonstrated in a randomized trial for patients with metastatic cancer and cord compression. Patients with hematologic malignant diseases were not included in this trial, however. An international multiinstitutional study on 172 patients with MM and cord compression found that radiation therapy without surgery resulted in improvement in motor function in 52% of patients.[66] This study showed that a more gradual development of motor deficits (>7 days) was associated with a better functional outcome than rapid development of motor dysfunction (1 day to 7 days). In a recent update from the same group, the overall survival in patients with MM receiving radiotherapy for cord compression was significantly associated with Eastern Cooperative Oncology Group (ECOG)-performance status ($p < 0.001$), preradiotherapy ambulatory status ($p < 0.001$), other osseous lesions ($p < 0.001$), and extraosseous lesions ($p < 0.001$).[66] One small series found that radiation therapy alone can be safe and effective even in the setting of spinal instability on radiographic images.[67] Patients with cord compression in whom radiation therapy is offered as first-line therapy should be placed on steroids before initiation of radiation therapy to reduce the risk of further neurologic compromise from acute radiation-related local inflammation.

Although plasma cell tumors are considered a radiosensitive entity, durable local control with adequate doses of radiation therapy may be important, especially in light of recent advances in MM therapy, resulting in longer life expectancies. In the multicenter study on patients with MM and cord compression described previously, it was found that long-course radiation therapy with higher BED (10 fractions of 3 Gy, 15 fractions of 2.5 Gy, and 20 fractions of 2 Gy) was associated with a significantly higher chance of motor function improvement than short-course radiation therapy (1 fraction of 8 Gy, 5 fractions of 4 Gy).[68] Motor function recovery at 1 year was found to be 76% versus 40% in patients who received long-course treatment versus short-course treatment ($p = 0.003$). In the updated study specifically addressing radiation dose fractionation and local control, there was a higher local control rate with long-course radiation therapy (10×3 Gy, 15×2.5 Gy, or 20×2 Gy) compared with short-course treatment (1×8 Gy or 5×4 Gy), with 2-year local control rates of 91% versus 68%, although the difference did not reach statistical significance ($p = 0.12$).[66] In a study from Germany on 138 patients with MM irradiated to 272 sites,[54] pain reduction was significantly lower in patients who received less than 30 Gy compared with those who received 40 Gy to 49 Gy (65% versus 92%; $p < 0.001$). On multivariable analysis for pain reduction, a daily fraction of 2 Gy was superior to daily doses of 4 Gy to 15 Gy (odds ratio [OR], 11; $p = 0.027$). Alcorn et al reported on 74 patients with MM irradiated to 117 sites to a median dose of 30 Gy, or a BED of 39 Gy.[69] At a median follow-up of 32 months, 26% recurred locally. On multivariable analysis, a BED of less than 39 Gy was significantly associated with increased local recurrence rates (OR, 2.8; $p = 0.03$). At our institution, commonly used radiation dose fractionation schemes for MM palliation include 37.5 Gy in 2.5-Gy fractions or 30 Gy in 10 fractions; although in patients with limited life expectancies, 20 Gy in 5 fractions or 8 Gy in 1 fraction can be considered.

FUTURE DIRECTIONS

Advances in our ability to treat MM and other monoclonal gammopathies depend ultimately on understanding the etiology and pathogenesis of these diseases. In the past decade, there has been an improvement in the understanding of the molecular and cellular biology of the myeloma clone. The cause of these diseases remains elusive, however, as does the identity of the myeloma precursor cell itself.

Advances in the clinical staging of MM, particularly with respect to prognostic factors such as clinical laboratory parameters, are allowing more rational decisions on appropriate therapy. Although progress has been made in the therapeutic management of MM in the past 30 years, particularly with the introduction of chemotherapy and promising results from transplant studies, curative therapy for all plasmacytomas and for MM remains to be defined. Radiotherapy combined with drugs continues to be an important modality in the treatment of MM. Much research remains to be done in finding the right schedules for transplantation, the best sources of hematopoietic stem cells, and optimal preparative regimens for transplantation.

The novel agents thalidomide, lenalidomide, and bortezomib are now first-line options for patients with both newly diagnosed and relapsed MM and provide a paradigm of drug development in MM. It is hoped that ongoing research efforts will provide additional insight regarding the optimal use of novel therapies as well as the role of other emerging new compounds with activity in MM, so as to maximize clinical benefit.

Until better therapies emerge based on an understanding of the biology of MM, clinical research in the next decade will continue to focus on more effective and less toxic drug and radiotherapy regimens. The need to find new therapeutic approaches to treat this disease remains one of the daunting challenges in oncology today.

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