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Multiple Myeloma

Jacob Laubach, Paul Richardson,
and Kenneth Anderson

Dana Farber Cancer Institute, Boston, Massachusetts 02115;
email: jacobp_laubach@dfci.harvard.edu

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Abstract

Multiple myeloma (MM) is a B cell neoplasm of the bone marrow with a complex array of clinical manifestations including anemia, bone lesions, hypercalcemia, renal dysfunction, and compromised immune function. It accounts for 10%–15% of all hematologic malignancies, and 20% of deaths related to cancers of the blood and bone marrow. The diagnosis of MM is based on the presence of neoplastic plasma cells in the bone marrow or other extramedullary sites, along with evidence of disease-related organ dysfunction. Although the disease remains incurable, significant advances in both basic and translational research have enhanced understanding of disease pathogenesis and guided the development of new and more effective therapies. These agents include the immunomodulatory drugs thalidomide and lenalidomide, the proteasome inhibitor bortezomib, and other therapeutics that are currently being evaluated. This review highlights important historical landmarks in the field of MM, examines the pathogenesis and clinical manifestations of the disease, and outlines principles of both diagnosis and treatment of MM.

INTRODUCTION

Multiple myeloma (MM) is a B cell neoplasm characterized by aberrant expansion of plasma cells within the bone marrow and extramedullary sites, including cortical bone. It accounts for 10%–15% of hematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow (1). In 2009, there were 20,580 new cases of MM in the United States and 10,580 deaths attributable to the disease (2). Management of the disease has changed dramatically in the past decade with the introduction of the immunomodulatory drugs thalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib. This review examines the pathogenesis of MM, clinical manifestations of the disease, and the diagnostic evaluation for MM, as well as key principles of patient management.

HISTORICAL LANDMARKS

A series of observations in the 1840s provided initial insight regarding the pathophysiology of MM. Examination of postmortem specimens obtained from patients afflicted by what is now recognized as MM led to descriptions of soft bones and infiltration of the bone marrow by large, oval cells with prominent nucleoli (3). Several years later, the British physician Henry Bence Jones characterized the abnormal urinary protein found in MM patients that now bears his name—the so-called Bence Jones protein (4). Plasma cells were first described in the late 1800s and later recognized as the malignant cell population underlying MM (5).

Over a century after the pioneering work of Dr. Bence Jones, Nobel prize-winning chemist Gerald Edelman and his student Joseph Gally showed the chemical similarity of urine Bence Jones proteins and serum light chains in MM patients, establishing a pivotal link between MM and abnormal immunoglobulin production (6). In his 1972 Nobel lecture (7), Dr. Edelman explained:

Some patients with multiple myeloma excrete urinary proteins which are antigenically

related to immunoglobulins but whose nature remained obscure since their first description by Henry Bence Jones in 1847. These Bence Jones proteins were most interesting, for they could be readily obtained from the urine in large quantities, were homogeneous, and had low molecular weights. It seemed reasonable to suggest that Bence Jones proteins represented one of the chains of the immunoglobulin molecule that was synthesized by the myeloma tumor but not incorporated into the homogenous myeloma protein and therefore excreted into the urine.

This hypothesis was corroborated one exciting afternoon when my student Joseph Gally and I heated solutions of light chains isolated from our own serum immunoglobulins in the classical test for Bence Jones proteinuria. They behaved as Bence Jones proteins, the solution first becoming turbid, then clearing upon further heating. A comparison of light chains of myeloma proteins with Bence Jones proteins by starch gel electrophoresis in urea and by peptide mapping confirmed the hypothesis.

The development of electrophoresis as a diagnostic modality allowed for protein separation and led to the identification of a characteristic narrow, “church-spire” peak in most patients with MM (8). Jan Waldenström utilized these methods to distinguish polyclonal from monoclonal gammopathies and characterize conditions associated with the latter, including MM, “benign monoclonal protein” (later termed monoclonal gammopathy of undetermined significance or MGUS), Waldenström macroglobulinemia, and AL-amyloidosis (9).

PATHOGENESIS

In recent years, understanding of MM pathogenesis has improved considerably with the application of molecular biological techniques. It is now understood that normal B cell differentiation occurs in early (antigen-independent) and late (antigen-dependent) stages, culminating in the production of plasma cells and memory B



cells (10, 11). During antigen-independent differentiation, precursor B cells undergo VDJ rearrangement and mature into naïve, resting B cells that circulate in the blood and lymphoid tissue. Upon encountering antigen with specificity for the immunoglobulin receptor, B cells aggregate in germinal centers and undergo somatic hypermutation and immunoglobulin class switch, producing high affinity IgG or IgA antibodies (12). A high degree of immunoglobulin heavy chain gene hypermutation is present in MM cells, suggesting that tumor cells derive from a postgerminal center B cell (13). Mutations occurring during immunoglobulin receptor somatic hypermutation and class switch are likely involved in the pathogenesis of MM.

Chromosomal abnormalities are detected in up to 90% of MM patients (14). Gain or loss of specific chromosomal regions is frequently observed, including monosomy or partial deletion of chromosome 13, loss of the short arm of chromosome 17 (where the tumor-suppressor gene TP53 resides), and gains or amplification of chromosomal region 1q (15). Patients are generally classified as being hyperdiploid (with the number of chromosomes ranging from 48–74) or nonhyperdiploid (16). Hyperdiploidy is most often the result of trisomy involving the odd-numbered chromosomes 3, 5, 7, 9, 11, 15, 19, and 21 (17). Nonhyperdiploid patients can be hypodiploid, near-diploid, or near-tetraploid. Primary translocations in MM typically involve the immunoglobulin heavy chain gene at the chromosome 14q32 locus along with partner genes such as *cyclin D1* (chromosome 11q13), *cyclin D3* (chromosome 6p21), *FGFR3/MMSET* (chromosome 4p16), and *C-MAF* (chromosome 16q23) (18). It is believed that such mutations lead to dysregulated growth of the affected clone. *C-MAF*, for example, appears to augment MM cell proliferation and binding to surrounding bone marrow stromal cells (BMSCs) (19). Inhibition of FGFR3, meanwhile, has been shown to promote plasma cell differentiation and induce apoptosis (20).

The pathogenesis of MM is also driven by critical interactions between MM cells and the bone marrow microenvironment, which

is composed of extracellular matrix (ECM) proteins, such as fibronectin, collagen, and laminin, along with cellular elements such as hematopoietic stem cells, immune cells, bone marrow endothelial cells, and BMSCs, as well as anatomically adjacent but functionally distinct modifiers of cortical bone, namely osteoclasts and osteoblasts. Adhesion of MM cells to ECM proteins and accessory cells leads to increased expression of factors such as interleukin-6 (IL-6), insulin-like growth factor, and vascular endothelial growth factor (VEGF), which in turn further stimulate growth and survival of the malignant clone (21, 22). Various intracellular pathways are involved in this response, including the Ras-Raf-MAPK kinase, MEK-extracellular signal-regulated kinase, phosphatidylinositol 3-kinase-Akt, and the Janus kinase 2-signal transducer and activator of transcription 3 pathways (23).

It is now understood that MM represents the late stage of an underlying plasma cell disorder that in the majority of patients begins with MGUS (24). MGUS is characterized by a low burden of disease and absence of organ dysfunction related to the underlying plasma cell clone. The annual rate of transformation from MGUS to MM or another malignant plasma cell disorder is approximately 1% (25). Patients with smoldering MM have a greater degree of disease involvement, as reflected by an increased serum paraprotein concentration (≥ 3 g/dl) and/or percentage of bone marrow plasma cells ($> 10\%$), but are without evidence of MM-related organ dysfunction (26). The annual rate of transformation from smoldering MM to MM is approximately 10% in the first five years following diagnosis (27), and the median time to progression appears to be two to three years (28–31). Sequential genetic events affecting various intracellular pathways appear to underlie the transformation from MGUS to MM (32).

CLINICAL MANIFESTATIONS

The classic clinical manifestations of MM include bone abnormalities, hypercalcemia,



anemia, renal impairment, recurrent infection, and peripheral neuropathy.

Bone Disease

Bone disease is present in up to 60% of MM patients at the time of diagnosis (33) and can manifest as lytic bone lesions, vertebral body compression fractures, or osteopenia/osteoporosis. Such lesions may or may not be associated with pain. Normal bone homeostasis is maintained by the activity of osteoblasts and osteoclasts. BMSCs and osteoblasts are involved in the regulation of osteoclastogenesis via production of receptor activator of NF κ B ligand (RANKL) and osteoprotegerin (OPG) (34). RANKL stimulates osteoclast activity and differentiation by binding RANKL on the surface of osteoclasts, whereas OPG inhibits this interaction by binding RANKL (35). Interaction between MM cells and BMSCs increases RANKL and decreases OPG levels, resulting in increased osteoclast activity (36). At the same time, osteoblast activity is inhibited via several mechanisms, including downregulation of the transcription factor RUNX2 (37). Together, these interactions lead to bone resorption, decreased new bone formation, and an increase in bone turnover.

Hypercalcemia

Hypercalcemia is the most common metabolic abnormality associated with MM, and occurs largely as a result of osteolysis and bone resorption, with efflux of calcium into the extracellular fluid (38). Renal impairment and increased renal tubular calcium reabsorption also contribute to this effect. The phenomenon appears to be unrelated to parathyroid hormone-related protein (PTHrP) levels, as MM is not typically associated with an increase in PTHrP concentration (38).

Anemia and Hematologic Abnormalities

Hematologic abnormalities frequently occur in association with MM. Anemia, leukopenia,

and thrombocytopenia can all occur, and MM should be considered in the differential diagnosis of patients with unexplained cytopenias. Anemia is most common and is observed in up to 70% of patients at the time of diagnosis (33). The anemia is typically normocytic and normochromic, although macrocytosis can occur as a result of rouleaux formation or underlying vitamin B12 deficiency, which in one series was reported in 13% of MM patients (39). Anemia in MM is often disproportionate to the degree of bone marrow infiltration by tumor cells, suggesting that factors other than replacement of normal hematopoietic tissue play a role in its development. These include suppression of erythroblast maturation by overexpression of Fas ligand and TNF-related apoptosis-inducing ligand (40) and an inadequate erythropoietin response.

Renal Impairment

Renal impairment affects 20%–30% of MM patients at the time of diagnosis and over 50% of patients at some point in the course of the disease (41). The mechanisms of MM-associated kidney injury are complex and multifaceted. The predominant mechanism of injury is related to accumulation of excess light chain within the distal tubule, where light chains interact with Tamm-Horsfall protein, leading to tubular cast formation and obstructive nephropathy. This phenomenon is referred to as myeloma kidney (42). Hypercalcemia, hyperuricemia, dehydration, nephrotoxic drugs (such as nonsteroidal anti-inflammatories), inadvertent use of contrast material, as well as AL amyloidosis or light chain deposition can also contribute to renal impairment in MM.

Recurrent Infection

MM patients are at increased risk for infection, particularly infections involving the upper respiratory system. This is due to deficiency in both humoral and cell-mediated immune function. The concentration of uninvolved immunoglobulins is frequently decreased at

diagnosis, and may remain suppressed throughout the patient's course. Chemotherapy reduces the number of CD4⁺ cells, an effect that may be prolonged following high-dose chemotherapy, and the concomitant use of corticosteroids as a component of therapy increases the risk of infection further. MM should be considered in the differential diagnosis of adults with frequent, recurrent infection.

Peripheral Neuropathy

Peripheral neuropathy is present in a significant percentage of MM patients at diagnosis and, in addition, represents an important toxicity related to various agents used in the treatment of the disease (43, 44). Patients with peripheral neuropathy at diagnosis typically show evidence of a length-dependent axonal sensorimotor neuropathy, which may involve all sensory modalities (45). Painful small fiber neuropathy may be present as well, but is less common.

DIAGNOSTIC EVALUATION

The diagnosis of MM is based on the presence of a monoclonal protein (M-protein) and/or significant plasma cell involvement within the bone marrow ($\geq 10\%$ of cellular bone marrow), along with evidence of end organ damage manifested by either bone abnormalities, elevated serum calcium (≥ 11.5 g/dl), renal

insufficiency (serum creatinine ≥ 2 mg/dl), or anemia (hemoglobin ≤ 10 g/dl or 2 g/dl below normal). MM should be differentiated from MGUS and smoldering MM (Table 1). As previously noted, MGUS is characterized by a serum M-protein concentration of < 3 g/dl, less than 10% bone marrow plasma cells, and the absence of organ damage related to the underlying plasma cell dyscrasia (46). Smoldering MM, meanwhile, is characterized by the absence of symptoms and MM-related organ impairment, but also by greater plasma cell bone marrow involvement ($\geq 10\%$ of cellular bone marrow) and/or M-protein concentration (≥ 3 g/dl) than MGUS.

Laboratory studies performed in the evaluation of a patient with suspected MM should include the comprehensive metabolic panel, complete blood count with differential, serum protein electrophoresis with immunofixation electrophoresis (IFE), 24-hour urine for both total protein and urine protein electrophoresis (UPEP) with IFE, quantitative immunoglobulins, serum-free light chain analysis, B₂-microglobulin, and lactate dehydrogenase. $\beta 2$ -microglobulin is a component of the major histocompatibility 1 complex and is a serum marker of tumor burden in lymphoid malignancies such as MM (47). The serum-free light chain assay allows for quantification of free, unbound light chain (48). Clonal production of either kappa or lambda light

Table 1 Diagnostic criteria for MGUS (monoclonal gammopathy of undetermined significance), MM (multiple myeloma), smoldering MM, and solitary plasmacytoma

Disorder	Criteria
Monoclonal gammopathy of undetermined significance	Serum monoclonal protein level < 3 g/dl and clonal bone marrow plasma cells $< 10\%$ Absence of plasma cell dyscrasia-related symptoms and end-organ damage (lytic bone lesions, anemia, hypercalcemia, or renal failure)
Smoldering multiple myeloma	Serum monoclonal protein level ≥ 3 g/dl and /or clonal bone marrow plasma cells $\geq 10\%$ Absence of plasma-cell dyscrasia-related symptoms and end-organ damage (lytic bone lesions, anemia, hypercalcemia, or renal failure)
Multiple myeloma	Serum and/or urine monoclonal protein and/or clonal bone marrow plasma cells Presence of plasma cell dyscrasia-related lytic bone lesions, anemia, hypercalcemia, or renal failure
Solitary plasmacytoma	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells No evidence of additional plasma-cell dyscrasia-related disease involvement (clonal bone marrow plasma cells, lytic bone lesions, anemia, hypercalcemia, or renal failure)

chain in the setting of an underlying plasma cell dyscrasia disrupts the normal ratio between these molecules. The serum-free light chain assay is utilized in combination with serum and urine electrophoresis with immunofixation to screen patients with suspected MM, monitor patients with oligosecretory disease, and to assess response to therapy (49).

A bone marrow aspiration and biopsy is an essential component of the diagnostic evaluation for MM. The marrow may show diffuse or focal plasma cell involvement (50). The plasma cells are often dysplastic, with prominent nucleoli and an increase in the nucleus to cytoplasmic ratio. Plasma cell clonality is established on the basis of either kappa or lambda light chain restriction. The presence of a clonal plasma cell population is determined using flow cytometry with anti- κ and anti- λ antibodies against cytoplasmic light chain or through immunohistochemical staining for cytoplasmic light chain. Clonality can be confirmed through detection of IgH chain gene rearrangement if necessary, but this is not a standard component of the evaluation. A Congo red stain should be obtained in cases where AL amyloidosis is suspected.

Cytogenetic analysis is performed using both conventional metaphase karyotype and fluorescence in situ hybridization (FISH) panel. FISH with probes for common MM-related mutations such as deletion (del) 13, del 17, translocation (t)(4;14), t(11;14), and t(14;16) is recommended (51). When available, gene expression profiling may be performed as part of the diagnostic evaluation to potentially aid in prognosis or as a research tool, and as its role is further refined through ongoing clinical studies, this modality will likely play an increasingly important role in the management of MM (52).

A skeletal survey of the skull, long bones, and ribs is performed as part of the diagnostic evaluation to assess for MM-related bone abnormalities. The sensitivity of plain films in detecting early MM bone lesions is a limitation of this approach. Computed tomography (CT) and magnetic resonance imaging (MRI) are more sensitive and should be considered for

certain patients, particularly those with musculoskeletal symptoms in the absence of discrete abnormalities on skeletal survey. The role of fluorodeoxyglucose (FDG)-PET imaging in the diagnosis and assessment of prognosis in MM is currently being assessed (53). Studies of FDG-PET suggest its ability to detect MM involvement is comparable to that of MRI, and it may be particularly effective in detecting occult sites of involvement. Finally, dual-energy X-ray absorptiometry (DEXA) represents a useful imaging modality given the risk of osteoporosis and associated bone events observed with the disease (54). A significant decrease in bone mineral density on DEXA study should prompt initiation of intravenous bisphosphonate therapy in patients with smoldering or early stage MM who would otherwise be monitored without therapy.

STAGING AND RISK STRATIFICATION

Once a diagnosis of MM has been established, the disease is classified according to the Durie-Salmon and International Staging System (ISS) criteria (**Table 2**). As with other tumor-specific staging systems, these provide insight regarding the extent and biological behavior of the disease. The Durie-Salmon stage is based on the hemoglobin concentration, calcium level, and serum/urine M-protein concentration as well as the extent of MM-associated bone disease at the time of diagnosis and, as such, reflects overall tumor burden (55). The ISS, however, is based on the concentration of serum β_2 -microglobulin and albumin, which emerged from multivariate analysis of clinical features from approximately 11,000 previously untreated MM patients as being predictive of survival (56). Patients are categorized as having stage I (median survival 62 months), stage II (median survival 44 months), or stage III (median survival 29 months) disease based upon treatments available at the time this study was conducted (including conventional chemotherapy, high-dose chemotherapy and stem cell transplantation, and thalidomide, but not the



Table 2 Staging systems for multiple myeloma

Stage	Durie-Salmon staging system (55)	International staging system (56)
I	All of the following: Hemoglobin >10 g/dl Serum calcium $\leq$ 12 mg/dL No myeloma-related bone lesions (solitary plasmacytoma excepted) Low M-protein concentration (IgG <5 g/dl, IgA <3 g/dl, and Bence Jones protein <4 g/24 h)	Beta-2 microglobulin <3.5 mg/L Albumin >3.5 g/dl
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: Hemoglobin <8.5 g/dl Serum calcium >12 mg/dL Extensive lytic bone lesions High M-protein concentration (IgG >7 g/dl, IgA >5 g/dl, or Bence Jones protein >12 g/24 h)	Beta-2 microglobulin >5.5 mg/L

Subclassification.

Normal renal function (serum creatinine <2.0 mg/dL).

Abnormal renal function (serum creatinine $\geq$ 2.0 mg/dL).

more recent novel therapies, such as lenalidomide and bortezomib).

Genetic abnormalities as determined by either conventional metaphase karyotype and/or FISH are also used to classify patients with MM. Hyperdiploidy and t(11;14) have been associated with standard risk disease, whereas hypodiploidy, t(4;14), t(14;16), t(14;20), and del(17p) have been associated with high-risk disease (57–59). When detected by metaphase karyotype, del(13) is also associated with high-risk disease (60).

Gene expression profiling based on microarray analysis of mRNA derived from CD138-enriched plasma cells has been evaluated as a means to classify patients with MM (61, 62). Although this approach is still considered investigational in MM and has not yet been widely implemented, it represents a powerful technique and will likely be incorporated in the classification of patients in the future.

MANAGEMENT

Timing of Therapy

Patients with MGUS, smoldering MM, and early stage asymptomatic MM are typically observed without therapy. Treatment with

systemic chemotherapy is indicated when disease-related symptoms or organ involvement develop. Systemic chemotherapy for smoldering MM, which is characterized by a relatively low disease burden, is an appealing concept and has been evaluated in a number of clinical trials. For example, melphalan plus prednisone was compared to initial observation with treatment at time of progression in one study involving 50 patients with smoldering MM (63). The response to therapy among those treated initially versus those treated at the time of progression to overt MM was similar, and there was no benefit in terms of overall survival associated with early therapeutic intervention. Thalidomide has also been assessed in smoldering MM, but drug toxicity—particularly peripheral neuropathy—has limited its application in this setting (64). Lenalidomide is currently being evaluated in smoldering MM. On the basis of available evidence, chemotherapy is generally not recommended for patients with smoldering MM outside the context of a clinical trial.

The intravenous bisphosphonates zoledronic acid and pamidronate do, on the other hand, play a role for many patients with smoldering and early stage MM. Although they do not appear to affect disease progression or

overall survival in this population of patients, these agents decrease the incidence of skeletal events (65, 66). Treatment with pamidronate or zoledronic acid should therefore be considered in smoldering MM when there is evidence of diminished bone density associated with the underlying plasma cell disorder.

Assessment of Treatment Response

Assessment of response to therapy is a critical component of overall disease management, as it provides insight regarding the sensitivity of the disease to chemotherapy, informs decisions regarding duration of therapy, and ensures uniformity of evaluation among providers, which is particularly important in multicenter clinical trials. The serum and/or urine M-protein concentrations are central to the evaluation of response. The pretreatment concentration is compared to levels observed at various time points during the course of therapy, with the result expressed in terms of percent change. The serum free light chain assay is also used in monitoring response and is particularly useful in patients with non- or oligo-secretory disease.

Bone marrow assessment is utilized when necessary. In the context of bone marrow evaluation, multiparameter flow cytometry (67) and real-time quantitative polymerase chain reaction (68) detect residual disease with a high level of sensitivity. They are not routinely performed and, indeed, not available at many treatment centers, but can be applied in circumstances that require this high level of sensitivity. A skeletal bone survey or more directed imaging study such as CT or MRI is used to monitor bone or soft tissue lesions in MM patients with extensive extramedullary disease.

The European Group for Blood and Marrow Transplantation (69) and the International Myeloma Working Group (70) have published criteria for assessment of response that are used in clinical practice. The International Myeloma Working Group response criteria are shown in **Table 3**.

General Approach to Therapy

Treatment decisions are influenced by a variety of patient-specific factors, including age, comorbid medical conditions, disease

Table 3 International Myeloma Working Group uniform response criteria (70)

Response subcategory	Response criteria
Complete response	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow
Stringent complete response	CR as defined above plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response	Serum and urine M-component detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria (2, 3) If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; VGPR, very good partial response.

characteristics, eligibility for autologous stem cell transplantation (SCT), and patient preferences. The aim of initial—or induction—therapy is arrest of tumor growth and MM-associated organ dysfunction. Treatment is administered with the additional aim of preparing the bone marrow for stem cell harvest in patients who are eligible for SCT. In those who are ineligible for SCT due to older age or comorbid conditions, therapy can be administered indefinitely in the absence of significant treatment-associated toxicities or to the point of best response followed by a treatment-free period. Transplant-eligible patients, however, are generally treated to the point of maximum response before undergoing stem cell mobilization and, thereafter, high dose therapy with stem cell support.

In the setting of relapsed disease, treatment decisions are again influenced by age, comorbid medical conditions, disease characteristics, eligibility for a second autologous transplantation, and consideration of allogeneic transplantation in selected, younger patients, typically with an available sibling, HLA-matched donor. The disease tends to become more chemotherapy-resistant over time, and as such patients with relapsed MM are unlikely to have significant treatment-free periods but instead require in most instances continuous therapy, with conversion from one treatment regimen to another at the time of each episode of disease progression.

Conventional Chemotherapy

Systematic evaluation of MM therapies began in the 1940s, with reports on the use of an ethyl carbamate, urethane, in the treatment of the disease (71). Evaluation of melphalan (72) and cyclophosphamide (73) demonstrated the activity of alkylating agents in MM. The corticosteroids prednisone (74) and, subsequently, dexamethasone (75), were also shown to have significant single-agent activity in MM. Combination chemotherapy, which was introduced during this time period in the treatment of other cancers, was first applied to MM in the late

1960s. In a pivotal trial comparing melphalan alone to melphalan plus prednisone, melphalan plus prednisone proved to be superior, as the combination was associated with disease remission in approximately 40% of patients and a six-month improvement in overall survival (76). Melphalan plus prednisone was thus established as a standard of care and remained a cornerstone in MM therapy for decades thereafter.

Efforts to improve treatment outcomes through addition of other chemotherapeutic drug classes such as anthracyclines to the backbone of corticosteroid and alkylator therapy prompted development of three-, four-, and five-drug combinations (77). However, though such regimens produced higher response rates than melphalan plus prednisone, they did not improve the duration of remission or overall survival (78, 79). The three-drug combination of vincristine, doxorubicin, and dexamethasone emerged as the preferred induction therapy regimen for patients eligible for SCT, minimizing the exposure of patients to alkylation prior to undergoing stem cell collection (80).

Novel Therapies in MM

The treatment of MM has changed dramatically in the past decade with the introduction of new drug classes with potent anti-MM activity, namely the immunomodulatory drugs thalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib. As a result of these advances, patient outcomes have improved substantially. Thalidomide, the first of the novel agents to be clinically evaluated in patients with MM, was in many respects an unlikely lead candidate for the new generation of MM therapy. Originally marketed in Europe in the 1950s and 1960s as a sedative, thalidomide gained widespread use in the treatment of hyperemesis gravidarum. It was subsequently linked with severe birth defects in as many as 10,000 infants (81) and thus banned in nearly all countries throughout the world. Because of its unique pharmacologic properties, however, thalidomide remained a drug of interest and ultimately proved to be effective in

diseases such as erythema nodosum leprosum and Behcet syndrome. The antiangiogenic properties of thalidomide (82) later provided the impetus for its assessment in MM, a disease characterized by heightened levels of circulating angiogenic cytokines, such as VEGF and increased bone marrow vascularity (83).

The initial clinical experience with thalidomide in MM was promising, as the agent demonstrated significant activity even in patients with heavily pretreated, relapsed and refractory disease (84). Subsequent studies in patients with newly diagnosed disease were also impressive. Thalidomide in combination with melphalan and prednisone was superior to melphalan plus prednisone alone (85), and thalidomide in conjunction with dexamethasone proved superior to high-dose dexamethasone as monotherapy (86). In order to address concerns regarding the teratogenicity of thalidomide, the agent is administered through the System for Thalidomide Education and Prescribing Safety (STEPS), a program instituted to prevent any teratogenicity with its use (87). Various thalidomide-containing regimens, including thalidomide plus dexamethasone, thalidomide plus melphalan and prednisone, and thalidomide plus bortezomib and dexamethasone, are now used in the treatment of newly diagnosed and relapsed MM. Important side effects associated with thalidomide include somnolence, constipation, peripheral neuropathy, and venous thromboembolism.

Efforts to minimize the toxicities associated with thalidomide prompted the development of lenalidomide, an immunomodulatory drug that shares the structural backbone of its parent compound but with elimination of a carbonyl group and addition of an amine. The activity of lenalidomide in MM derives from several mechanisms, including stimulation of apoptosis, inhibition of angiogenesis, activation of tumor-suppressing CD4⁺/CD8⁺ T cells and NK cells (88), and modulation of interactions between MM cells and BMSCs. The clinical activity of lenalidomide in MM was confirmed in two large, randomized phase III studies in relapsed MM, wherein the combination of

lenalidomide and dexamethasone was superior to dexamethasone (89, 90). Lenalidomide-containing regimens such as lenalidomide plus dexamethasone, lenalidomide plus melphalan and prednisone, and lenalidomide plus bortezomib and dexamethasone are currently being evaluated in patients with newly diagnosed disease. Lenalidomide is less sedating than thalidomide and rarely causes significant peripheral neuropathy. However, the agent is more myelosuppressive than thalidomide, and blood counts must be closely monitored, particularly in patients with significant cytopenias prior to therapy and those with renal dysfunction. Like its parent compound, lenalidomide is also associated with an increased risk of venous thromboembolic events.

The boronic acid dipeptide small molecule bortezomib inhibits the ubiquitin-proteasome pathway, which plays an important role in intracellular protein homeostasis by regulating protein degradation and in turn modulating such critical cellular processes as cell cycle control, antigen processing, and apoptosis. Various mechanisms account for the activity of bortezomib in MM, including induction of apoptosis, inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), disruption of IL-6 induced signaling pathways, and cleavage of DNA repair enzymes (91). Phase I/II clinical trials demonstrated the tolerability and activity of single-agent bortezomib in relapsed and refractory disease, paving the way for a phase III that confirmed the efficacy of bortezomib in relapsed MM (92). In the setting of newly diagnosed disease, bortezomib plus melphalan and prednisone proved to be markedly more effective than melphalan and prednisone alone (93). Bortezomib-containing regimens have thus emerged as important therapeutic options for patients with both newly diagnosed and relapsed MM. Important toxicities associated with bortezomib include peripheral neuropathy, thrombocytopenia, and reactivation of herpes zoster as shingles.

It is important to emphasize that after over 30 years in which various treatment strategies offered no significant progression-free

or overall survival advantage over melphalan plus prednisone, multiple combinations involving thalidomide, lenalidomide, and bortezomib have now eclipsed the previous standard with respect to most, if not all, important clinical benchmarks (94).

Stem Cell Transplantation

The use of high-dose therapy followed by stem cell engrafting represents another important advance in the field of MM therapeutics. McElwain and colleagues pioneered autologous SCT in patients with MM and, together with other investigators, demonstrated that high-dose therapy with autologous SCT can overcome drug resistance in patients who had become refractory to conventional chemotherapy (95). Promising results in patients with relapsed and refractory MM provided the impetus for application of the technique at an earlier juncture in treatment. In an important clinical trial by Attal and colleagues, patients with newly diagnosed MM received either conventional induction therapy or conventional therapy followed by autologous SCT (96). SCT improved rates of response as well as five-year event-free survival and overall survival. SCT has consistently been associated with improvement in progression-free survival, although the impact of high-dose therapy on overall survival is less clear, as some studies have demonstrated a survival benefit while others have not (97). It is likely that autologous SCT will be refined further in the coming years as insight is acquired on how best to utilize this approach in conjunction with thalidomide, lenalidomide, and bortezomib.

Allogeneic SCT has also been employed in the treatment of MM. It offers the advantage of both a cytoreductive effect and a graft-versus-myeloma effect. The technique has resulted in durable responses, and long-term survival following allogeneic SCT has been documented (98). However, fully ablative allogeneic SCT in MM has been associated with prohibitively high rates of transplant-related mortality that limit its applicability in this setting.

Reduced-intensity conditioning allogeneic SCT is now being explored and may prove to be less toxic, and thus more effective, than myeloablative conditioning. At this time, allogeneic SCT is reserved primarily for younger patients with an HLA-identical sibling and is ideally administered as part of a clinical trial.

Adjunctive Therapy and Supportive Care

As a final point, the importance of supportive care in the management of MM cannot be overstated. Given the extent of MM-related bone involvement, for example, intravenous bisphosphonate therapy with either zoledronic acid or pamidronate is a crucial component of therapy as these agents decrease the frequency of skeletal events (99, 100). Timely referral to surgical and/or radiation oncology specialists is often necessary when managing complicated musculoskeletal manifestations of the disease such as paraspinal plasmacytoma, vertebral body collapse with spinal cord impingement, and destruction of long bone cortex with impending pathological fracture. Pain control figures prominently in the management of many patients who develop symptoms related to either musculoskeletal processes or peripheral neuropathy. Maintenance of up-to-date vaccine schedules lessens the risk of communicable infections such as influenza and pneumonia. Finally, appropriate referral to mental health specialists such as psychiatrists or psychologists enhances the ability of the patient to cope with the stresses inherent to the diagnosis and management of cancer.

SUMMARY AND CONCLUSIONS

Multiple myeloma is a B cell neoplasm of the bone marrow with a complex range of associated clinical manifestations, including anemia and other cytopenias, bone lesions, renal dysfunction, compromised immune function, and peripheral neuropathy. The diagnosis is based on the presence of clonal plasma cells in the bone marrow or extramedullary sites

in conjunction, serum and/or urine paraprotein, and disease-associated bone marrow, metabolic, renal, or bone dysfunction. The outcome for patients with MM has been enhanced dramatically in the past decade owing to the development and use of thalidomide, lenalidomide, and bortezomib, all of which target unique aspects of MM biology, and

there is great promise in the future for further advances based upon the translation of research findings from the bench to the bedside. The care of patients with the disease requires a comprehensive and coordinated approach that incorporates systemic chemotherapy as well as important adjunctive and supportive therapies.

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