REVIEW ARTICLE

MEDICAL PROGRESS

Multiple Myeloma

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Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction.[1] It accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers. In Western countries, the annual age-adjusted incidence is 5.6 cases per 100,000 persons.[2] The median age at diagnosis is approximately 70 years; 37% of patients are younger than 65 years, 26% are between the ages of 65 and 74 years, and 37% are 75 years of age or older.[2,3] In recent years, the introduction of autologous stem-cell transplantation and the availability of agents such as thalidomide, lenalidomide, and bortezomib have changed the management of myeloma and extended overall survival.[3-5] In patients presenting at an age under 60 years, 10-year survival is approximately 30%.[4]

THE BIOLOGY OF MULTIPLE MYELOMA

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal-center B cells. Multistep genetic and microenvironmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma (Fig. 1).[6] Several genetic abnormalities that occur in tumor plasma cells play major roles in the pathogenesis of myeloma.[7]

Primary early chromosomal translocations occur at the immunoglobulin switch region on chromosome 14 (q32.33), which is most commonly juxtaposed to *MAF* (t[14;16][q32.33;23]) and *MMSET* on chromosome 4p16.3. This process results in the deregulation of two adjacent genes, *MMSET* in all cases and *FGFR3* in 30% of cases.[6,8] Secondary late-onset translocations and gene mutations that are implicated in disease progression include complex karyotypic abnormalities in *MYC*, the activation of *NRAS* and *KRAS*, mutations in *FGFR3* and *TP53*, and the inactivation of cyclin-dependent kinase inhibitors CDKN2A and CDKN2C.[6,8] Other genetic abnormalities involve epigenetic dysregulation, such as alteration in microRNA expression and gene methylation modifications.[9] Gene-expression profiling allows classification of multiple myeloma into different subgroups on the basis of genetic abnormalities.[10] (The full names of the genes used in the text are provided in the Glossary in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Genetic abnormalities alter the expression of adhesion molecules on myeloma cells, as well as responses to growth stimuli in the microenvironment (Fig. 2). Interactions between myeloma cells and bone marrow cells or extracellular matrix

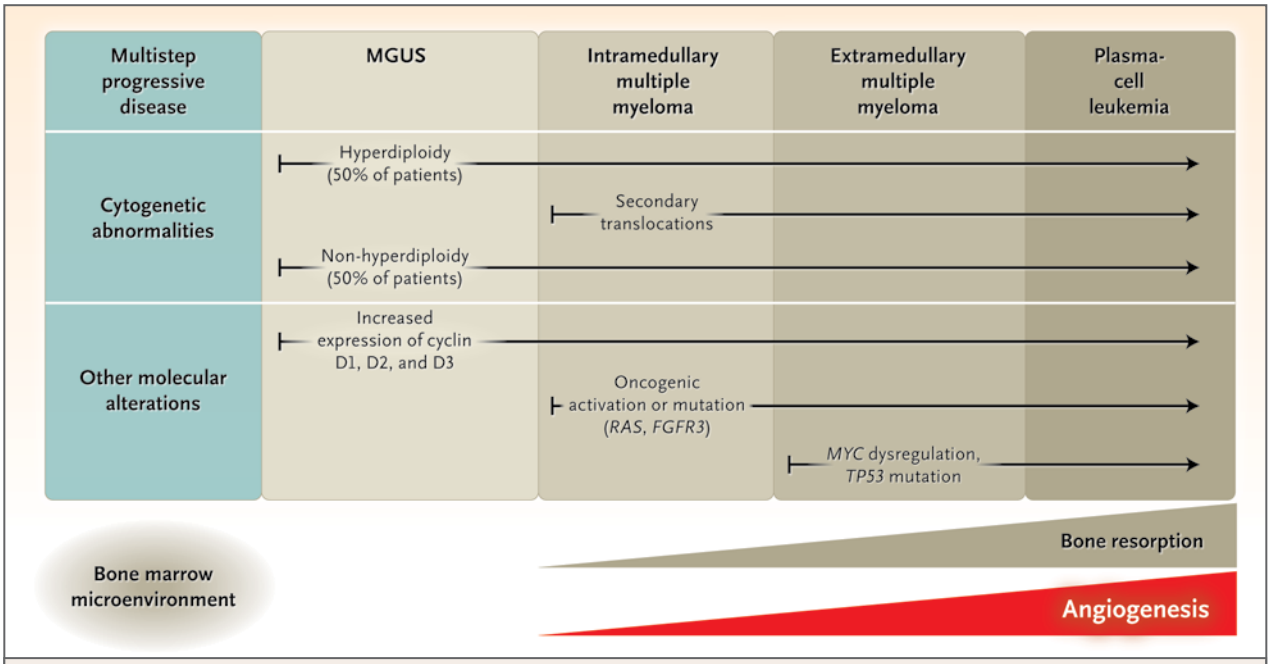

Figure 1. Multistep Pathogenesis of Multiple Myeloma.

Early chromosomal abnormalities (immunoglobulin heavy chain translocations or trisomies) are shared by plasma cells in multiple myeloma and in monoclonal gammopathy of undetermined clinical significance (MGUS). Secondary translocations involving *MYC* (8q24), *MAFB* (20q12), and *IRF4* (6p25) are common in multiple myeloma but quite rare in MGUS. Mutations of *RAS* or *FGFR3, MYC* dysregulation, deletion in p18, or loss of expression or mutation in *TP53* are found only in multiple myeloma and play a key role in determining tumor progression and drug resistance. Also, changes in gene expression, in particular the up-regulation of transcription factors, have been reported in plasma cells from patients with MGUS but not in those from patients with multiple myeloma. Besides molecular alterations of plasma cells, abnormal interactions between plasma cells and bone marrow, as well as aberrant angiogenesis, are hallmarks of disease progression.

proteins that are mediated through cell-surface receptors (e.g., integrins, cadherins, selectins, and cell-adhesion molecules) increase tumor growth, survival, migration, and drug resistance. The adhesion of myeloma cells to hematopoietic and stromal cells induces the secretion of cytokines and growth factors, including interleukin-6, vascular endothelial growth factor (VEGF), insulin-like growth factor 1, members of the superfamily of tumor necrosis factor, transforming growth factor β1, and interleukin-10. These cytokines and growth factors are produced and secreted by cells in the bone marrow microenvironment, including myeloma cells, and regulated by autocrine and paracrine loops.[11]

The adhesion of myeloma cells to extracellular matrix proteins (e.g., collagen, fibronectin, laminin, and vitronectin) triggers the up-regulation of cell-cycle regulatory proteins and anti-apoptotic proteins.[12] Bone lesions are caused by an imbalance in the function of osteoblasts and osteoclasts. The inhibition of the Wnt pathway suppresses osteoblasts, whereas the amplification of the RANK pathway and the action of macrophage inflammatory protein 1 α (MIP1α) activate osteoclasts.[13] The induction of proangiogenic molecules (e.g., VEGF) enhances the microvascular density of bone marrow and accounts for the abnormal structure of myeloma tumor vessels.[12]

The antimyeloma activity of proteasome inhibitors and immunomodulatory drugs arises from the disruption of multiple signaling pathways that support the growth, proliferation, and survival of myeloma cells. Proteasome inhibition stimulates multiple apoptotic pathways, including the induction of the endoplasmic reticulum stress response, and through the inhibition of nuclear factor κB (NF-κB) signaling down-regulates angiogenesis factors, cytokine signaling, and

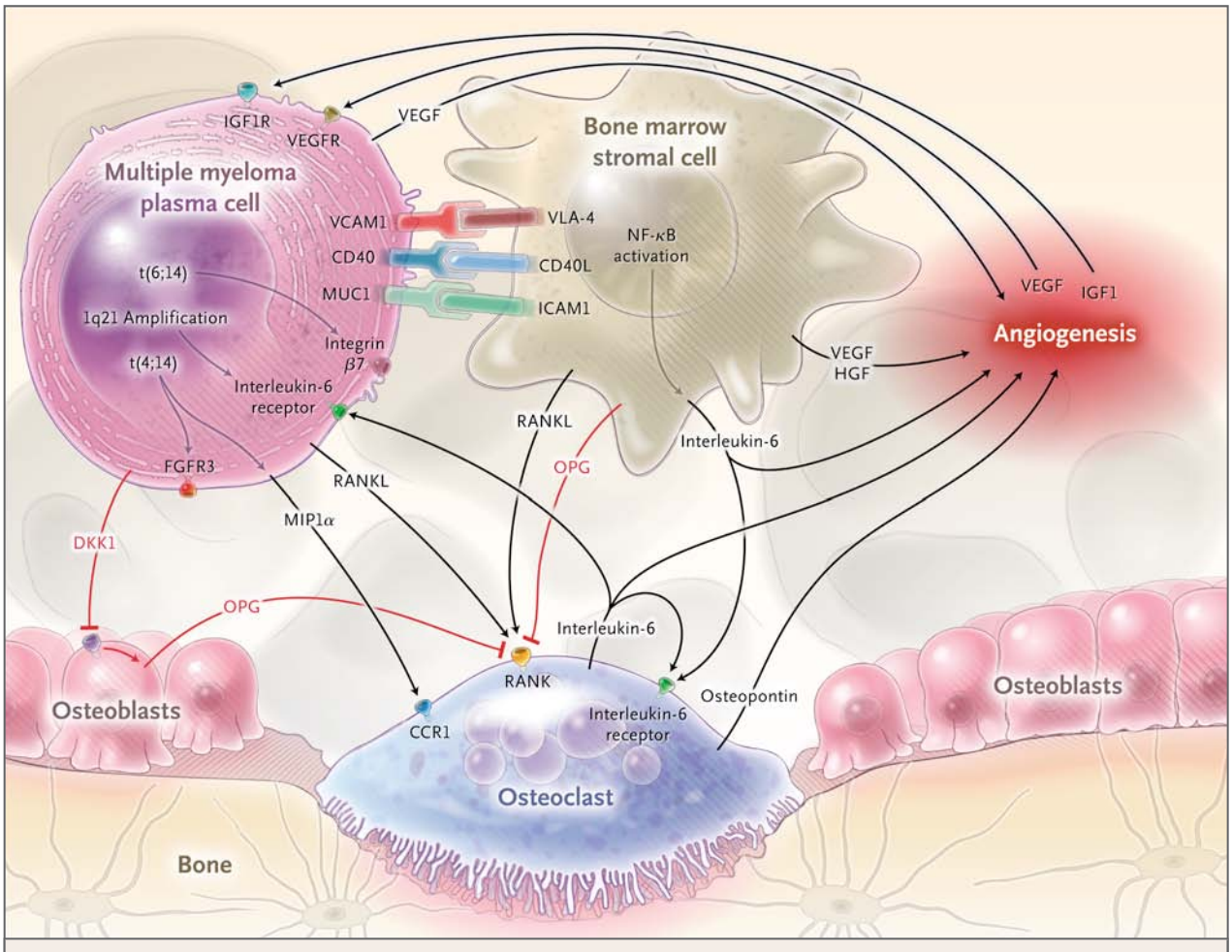

Figure 2. Interaction between Plasma Cells and Bone Marrow in Multiple Myeloma.

As part of the interaction between plasma cells and stromal cells, adhesion is mediated by cell-adhesion molecules, such as vascular-cell adhesion molecule 1 (VCAM1) and integrin alpha 4 (VLA-4). This interaction increases the production of growth factors, such as interleukin-6 and vascular endothelial growth factor (VEGF), which stimulates both plasma cells and angiogenesis. The increased osteoclast activity is due to an imbalance in the ratio between receptor activator of nuclear factor κB (RANK) and osteoprotegerin (OPG) as a result of enhanced production of RANK ligand (RANKL) and reduced production of OPG. Osteoblast activity is also suppressed by the production of dickkopf homolog 1 (DKK1) by plasma cells. Moreover, plasma cells can inhibit a key transcription factor for osteoblasts, runt-related transcription factor 2, causing a reduction in differentiation from precursors to mature osteoblasts. The adhesion of plasma cells to stromal cells up-regulates many cytokines with angiogenic activity, in particular interleukin-6 and VEGF. Osteoclasts that are activated by stromal cells can also sustain angiogenesis by secreting osteopontin. Chromosomal abnormalities can cause overproduction of receptors on myeloma cells. The 1q21 amplification causes an increase in interleukin-6 receptor and consequently an increase in growth mediated by interleukin-6. CCR1 denotes chemokine receptor 1, CD40L (or CD40LG) CD40 ligand, FGFR3 fibroblast growth factor receptor 3, HGF hepatocyte growth factor, ICAM1 intercellular adhesion molecule 1, IGF1 insulin-like growth factor 1, MIP1α macrophage inflammatory protein 1 α, MUC1 cell-surface–associated mucin 1, and NF-κB nuclear factor κB.

cell adhesion in the microenvironment.[14] Immunomodulatory drugs stimulate apoptosis and inhibit angiogenesis, adhesion, and cytokine circuits; they also stimulate an enhanced immune response to myeloma cells by T cells and natural killer cells in the host.[15]

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

The diagnosis of myeloma is based on the presence of at least 10% clonal bone marrow plasma cells and monoclonal protein in serum or urine.

In patients with true nonsecretory myeloma, the diagnosis is based on the presence of 30% monoclonal bone marrow plasma cells or a biopsy-proven plasmacytoma.[16] Myeloma is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction, including hypercalcemia, renal insufficiency, anemia, and bone disease (Table 1).[16-18] Anemia, which is present in about 73% of patients at diagnosis, is generally related to myeloma marrow infiltration or renal dysfunction.[19] Bony lesions develop in almost 80% of patients with newly diagnosed disease; in one study, 58% of patients reported bone pain.[20] Renal impairment occurs in 20 to 40% of patients with newly diagnosed disease,[20,21] mainly as a result of direct tubular damage from excess protein load, dehydration, hypercalcemia, and the use of nephrotoxic medications.[22] The risk of infection is increased with active disease but decreases with response to therapy.[23] Hypercalcemia is uncommon.[20]

The recommended tests for the diagnosis of myeloma include the taking of a detailed medical history and physical examination, routine laboratory testing (complete blood count, chemical analysis, serum and urine protein electrophoresis with immunofixation, and quantification of monoclonal protein), and bone marrow examination (trephine biopsy plus aspirate for cytogenetic analysis or fluorescence in situ hybridization [FISH]).[18,24] Conventional radiography of the spine, skull, chest, pelvis, humeri, and femora remains the standard to identify myeloma-related bone lesions. Magnetic resonance imaging (MRI) is recommended to evaluate symptoms in patients with normal results on conventional radiography and in all patients with radiographs suggesting the presence of solitary plasmacytoma of the bone. Computed tomography and MRI are the procedures of choice to assess suspected cord compression and should be performed on an urgent basis.[18,25]

Additional studies include staging of the disease, according to the International Staging System, which defines three risk groups on the basis of serum β_2-microglobulin and albumin levels.[26] Any chromosomal abnormality that is detected on standard cytogenetic analysis is associated with a worse outcome than that associated with a normal karyotype.[24] Specific translocations in the immunoglobulin heavy chain region that are detected on FISH, such as t(4;14), deletion 17p13, and chromosome 1 abnormalities, are associated with a poor prognosis.[7] Recently, gene-expression profiling and gene copy-number alterations have shown a promising prognostic role that needs to be validated in larger studies.[24] High-risk disease and poor prognosis are defined by the presence of one of the following in each category: hypodiploidy, t(4;14), or deletion 17p13; high levels of serum β_2-microglobulin or lactate dehydrogenase; and International Staging System stage III. Standard-risk disease is defined by the presence of hyperdiploidy or t(11;14), normal levels of serum β_2-microglobulin or lactate dehydrogenase, and International Staging System stage I.[24,26,27]

TREATMENT

STRATEGIES

Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires only clinical observation, since early treatment with conventional chemotherapy has shown no benefit.[1,28,29] Investigational trials are currently evaluating the ability of immunomodulatory drugs to delay the progression from asymptomatic to symptomatic myeloma. The treatment strategy is mainly related to age.[30] Current data would support the initiation of induction therapy with thalidomide, lenalidomide, or bortezomib plus hematopoietic stem-cell transplantation for patients under the age of 65 years who do not have substantial heart, lung, renal, or liver dysfunction.[31] Autologous stem-cell transplantation with a reduced-intensity conditioning regimen should be considered for older patients or those with coexisting conditions.[32,33] Conventional therapy combined with thalidomide, lenalidomide, or bortezomib should be administered in patients older than 65 years of age.[33] Less intensive approaches that limit toxic effects or prevent treatment interruption that would reduce the intended treatment effect should be considered in patients over 75 years of age or in younger patients with coexisting conditions. Biologic age, which may differ from chronologic age, and the presence of coexisting conditions should determine treatment choice and drug dose.

Treatment strategies should include the use of

Table 1. Diagnostic Criteria, Diagnostic Evaluation, and Staging System for Multiple Myeloma.

Diagnostic criteria
Diagnosis of myeloma
At least 10% clonal bone marrow plasma cells
Serum or urinary monoclonal protein
Myeloma-related organ dysfunction (CRAB criteria)
Hypercalcemia (serum calcium >11.5 mg/dl [2.88 mmol/liter])
Renal insufficiency (serum creatinine >2 mg/dl [177 μmol/liter])
Anemia (hemoglobin <10 g/dl or >2 g/dl below the lower limit of the normal range)
Bone disease (lytic lesions, severe osteopenia, or pathologic fracture)
Diagnostic evaluation
Diagnosis
Medical history and physical examination
Routine testing: complete blood count, chemical analysis with calcium and creatinine, serum and urine protein electrophoresis with immunofixation, quantification of serum and urine monoclonal protein, measurement of free light chains
Bone marrow testing: trephine biopsy and aspirate of bone-marrow cells for morphologic features; cytogenetic analysis and fluorescence in situ hybridization for chromosomal abnormalities
Imaging: skeletal survey, magnetic resonance imaging if skeletal survey is negative
Prognosis
Routine testing: serum albumin, β_2-microglobulin, lactate dehydrogenase
Staging
International Staging System
Stage I: serum β_2-microglobulin <3.5 mg/liter, serum albumin ≥3.5 g/dl
Stage II: serum β_2-microglobulin, <3.5mg/liter plus serum albumin <3.5 g/dl; or serum β_2-microglobulin 3.5 to <5.5 mg/liter regardless of serum albumin level
Stage III: serum β_2-microglobulin ≥5.5 mg/liter
Chromosomal abnormalities
High-risk: presence of t(4;14) or deletion 17p13 detected by fluorescence in situ hybridization
Standard-risk: t(11;14) detected by fluorescence in situ hybridization

induction regimens that are associated with high rates of complete response, followed by maintenance treatment. This approach combines maximal tumor reduction with continuous treatment, which is essential in delaying tumor regrowth. The level of response, and in particular achievement of complete response, is associated with an improved long-term outcome. A complete response is defined as the elimination of detectable disease on routine testing.[16-18] More stringent criteria, such as the quantification of free immunoglobulin light chains in the serum,[34] the quantification of bone marrow myeloma cells on multiparameter flow cytometry, and the identification of residual tumor cells on polymerase-chain-reaction assay, have been explored to define minimal residual disease, which is one of the most important independent prognostic factors for survival.[35,36] Younger patients who have a complete response after autologous transplantation have prolonged progression-free and overall survival.[37,38] In a retrospective analysis of 1175 patients who received combination therapy with melphalan and prednisone and either bortezomib or thalidomide, patients who had a complete response had a 75% reduction in the risk of death after a median follow-up of 29 months, as compared with those who did not.[39] Consolidation with two to four cycles of combination therapies and maintenance therapy with single agents until the time of disease progression have the potential to improve the outcome. Consolidation therapy after autologous transplantation with bortezomib- or lenalidomide-based regimens significantly improves the rate of complete response.[32,36] Maintenance treatment with thalidomide, although limited by the occurrence of peripheral neuropathy,[40-44] or with the more recently available drug lenalidomide, improved progression-free survival in younger and elderly patients.[45-47]

Recent therapeutic trends favor adapting the treatment for a specific patient according to that patient's risk factors. Although such risk-adapted strategies have not been prospectively validated, some investigators have recommended the use of bortezomib-containing regimens for high-risk disease and lenalidomide- or thalidomide-containing regimens for standard-risk disease.[27,48,49] These recommendations are based on evidence that patients with t(4;14) who received combination therapy with lenalidomide and dexamethasone had shorter overall survival than those without t(4;14).[50] In contrast, bortezomib induction improved survival for patients with t(4;14) but not for those with deletion 17p13.[51]

INDUCTION THERAPIES IN PATIENTS ELIGIBLE FOR TRANSPLANTATION

A detailed description of induction therapies[52-76] is provided in Table 2 and in Table 1 in the Supplementary Appendix. An overview of approaches to treatment is shown in Figure 3. The introduction of thalidomide, lenalidomide, or bortezomib into induction regimens has increased the rates of complete response. Three to six cycles of induction treatment are recommended.[31]

Table 2. Commonly Used Therapy Regimens in Newly Diagnosed Multiple Myeloma.

Regimen	Schedule	Complete Response Rate after Induction	Progression-free Survival	Overall Survival	Serious Toxic Effects Occurring in ≥10% of Patients
		%			
Bortezomib–dexamethasone	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk for a total of 4–8 cycles; dexamethasone: 40 mg/day given orally on days 1–4 and 9–12 every 3 wk for a total of 4–8 cycles[53]	21*	Median, 36 mo	At 3 yr, 81%	Infection (10%)
Bortezomib–dexamethasone–cyclophosphamide	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11 every 4 wk for a total of 4–12 cycles; dexamethasone: 40 mg/day given orally on days 1–4, 9–12, and 17–20 or on days 1, 2, 4, 5, 8, 9, 11, 12 every 4 wk for a total of 4–12 cycles; cyclophosphamide: 300 mg/m^2 given orally on days 1, 8, 15, 22 every 4 wk for a total of 4–12 cycles[56]	46*	Not reported	Not reported	Thrombocytopenia (25%), neutropenia (13%), anemia (12%), hyperglycemia (13%)
Bortezomib–dexamethasone–lenalidomide	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk for a total of 4–8 cycles; dexamethasone: 20 mg/day given orally on days 1, 2, 4, 5, 8, 9, 11, 12 every 3 wk for a total of 4–8 cycles; lenalidomide: 25 mg/day given orally on days 1–14 every 3 wk for a total of 4–8 cycles[58]	29	At 18 mo, 75%	At 18 mo, 97%	Lymphopenia (14%)
Lenalidomide–dexamethasone	Lenalidomide: 25 mg/day given orally on days 1–21 every 4 wk for a total of 4 cycles or until progression or intolerance; dexamethasone: 40 mg/day given orally on days 1, 8, 15, 22 every 4 wk for a total of 4 cycles or until progression or intolerance[54]	24†	Median, 25 mo	At 1 yr, 96%	Neutropenia (20%),deep-vein thrombosis (12%)
Melphalan–prednisone–thalidomide	Melphalan: 0.15 mg/kg given orally on days 1–7 every 4 wk for a total of 6 cycles[66] or 0.25 mg/kg on days 1–4 every 6 wk for a total of 12 cycles[67]; prednisone: 1.5 mg/kg given orally on days 1–7 every 4 wk for a total of 6 cycles[66] or 2 mg/kg on days 1–4 every 6 wk for a total of 12 cycles[67]; thalidomide: 100 mg/day given orally continuously until progression or intolerance[66] or 200 mg/day continuously for a total of 12 cycles of 6 wk[67]	13–16	Median, 22–28 mo	Median, 45–52 mo	Neutropenia (16–50%), deep-vein thrombosis (12%), peripheral neuropathy (6–10%), infection (10–13%)
Melphalan–prednisone–bortezomib	Melphalan: 9 mg/m^2 given orally on days 1–4 every 5–6 wk for a total of 9 cycles[73,76]; prednisone: 60 mg/m^2 given orally on days 1–4 every 5–6 wk for a total of 9 cycles[73,76]; bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1–4) and on days 1, 8, 22, 29 (cycles 5–9) every 6 wk for a total of 9 cycles[73] or 1.3 mg/m^2 on days 1, 8, 15, 22 every 5 wk for a total of 9 cycles[76]	24–30	Median, 22–27 mo	At 2 yr, 85–87%	Neutropenia (28–40%), thrombocytopenia (20–37%), anemia (10–19%), peripheral sensory neuropathy (5–14%)
Melphalan–prednisone–lenalidomide	Melphalan: 0.18 mg/kg given orally on days 1–4 every 4 wk for a total of 9 cycles; prednisone: 2 mg/kg given orally on days 1–4 every 4 wk for a total of 9 cycles; lenalidomide: 10 mg/day given orally on days 1–21 every 4 wk for a total of 9 cycles; by the 10th cycle, maintenance with lenalidomide at 10 mg/day on days 1–21 every 4 wk until progression or intolerance[47]	16	At 2 yr, 55%	At 2 yr, 82%	Neutropenia (71%), anemia (24%), thrombocytopenia (38%), infection (10%)

* In these trials, the response is reported as immunofixation-negative complete response plus immunofixation-positive complete response.
† In this trial, the response is reported as immunofixation-negative complete response plus very good partial response.

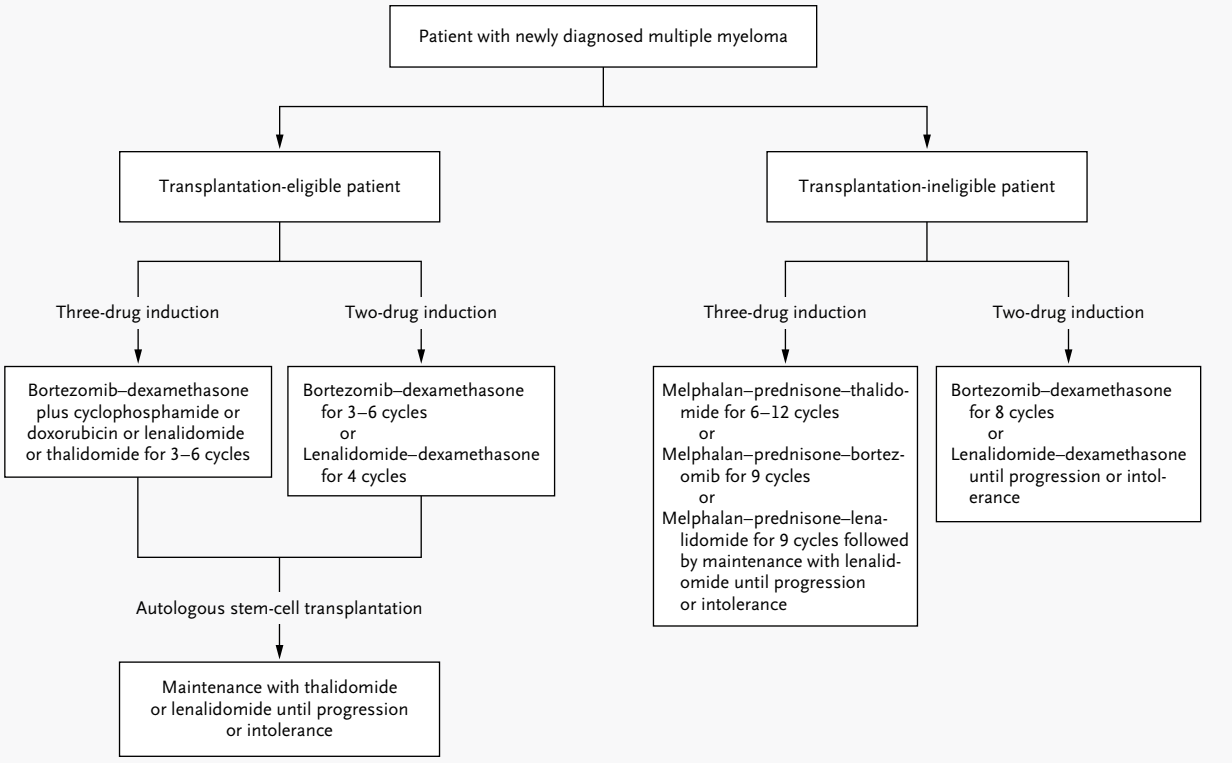

Figure 3. Suggested Approach to the Treatment of Newly Diagnosed Multiple Myeloma.

Several of the listed drug regimens are currently being evaluated in investigational trials. These include combination induction therapy with bortezomib and dexamethasone plus cyclophosphamide or lenalidomide, maintenance therapy with thalidomide or lenalidomide in younger patients, and melphalan–prednisone–lenalidomide followed by maintenance therapy with lenalidomide in elderly patients. If autologous stem-cell transplantation is delayed until the time of relapse, bortezomib-based regimens should be continued for eight cycles, whereas lenalidomide-based regimens should be continued until disease progression or the development of intolerable side effects.

Combination therapy with dexamethasone plus thalidomide,[52] bortezomib,[53] or lenalidomide[54] has been extensively used as an induction regimen before autologous stem-cell transplantation and has led to rates of nearly complete response of 8%, 15%, and 16%, respectively. More recently, three-drug combinations of bortezomib–dexamethasone plus doxorubicin,[55] cyclophosphamide,[56] thalidomide,[57] or lenalidomide[58] have been introduced, with rates of nearly complete response of 7%, 39%, 32%, and 57%, respectively. In a randomized study, combination therapy with bortezomib, thalidomide, and dexamethasone was superior to therapy with thalidomide plus dexamethasone with respect to both response rate and progression-free survival.[57] The dose of dexamethasone in such regimens may vary, and although the extent and rapidity of response are increased with a more dose-intense schedule, survival is not improved because of a significantly higher risk of toxic effects.[54] The use of high-dose dexamethasone (480 mg per month) should be limited to patients with life-threatening hypercalcemia, spinal cord compression, incipient renal failure, or extensive pain; otherwise, a lower dose (160 mg per month) should be considered.[31,54]

So-called total therapy programs, which utilize all available agents as induction, followed by two cycles of high-dose therapy (melphalan at a dose of 200 mg per square meter) and reinfusion of autologous peripheral-blood stem cells (tandem transplantation), have achieved 4-year rates of event-free survival of up to 78%,[59] but there is no randomized study to support these results. The advantage of tandem over single transplantation is still unclear.[60,61] Single transplantation

appears to be a more suitable option for most patients, since high response rates can be achieved with induction regimens that include thalidomide, lenalidomide, or bortezomib and may be further enhanced by post-transplantation consolidation and maintenance therapies.[31] Intermediate-dose melphalan (100 to 140 mg per square meter of body-surface area), followed by autologous transplantation, can be used in patients between the ages of 65 and 70 years or in younger patients with coexisting conditions.[32,33]

Overall survival is similar whether transplantation is performed at diagnosis or at the time of relapse, although early transplantation significantly prolongs progression-free survival, as well as the period of time without symptoms, treatment, and treatment-related toxic effects.[62] A prospective clinical trial is evaluating the effect of delayed transplantation after induction with combinations containing thalidomide, lenalidomide, or bortezomib.[63]

Allogeneic transplantation should be performed infrequently outside clinical trials, given the high risk of death and complications. However, in selected patients, it may achieve long-term disease control. Trials comparing allografting with autografting have had conflicting results. In high-risk patients, no significant differences in outcome were seen.[64] In 162 patients with newly diagnosed disease, increased event-free survival and overall survival were reported in patients undergoing autologous–allogeneic transplantation (tandem transplantation in which autologous transplantation is followed by a second transplantation with a graft from a qualified HLA-identical sibling, when available), as compared with double autologous transplantation, when no sibling was available.[65]

INDUCTION THERAPIES IN PATIENTS NOT ELIGIBLE FOR TRANSPLANTATION

A meta-analysis of studies involving 1685 patients who were enrolled in six randomized studies comparing melphalan plus prednisone with or without thalidomide[66-71] showed that the addition of thalidomide increased median progression-free survival by 5.4 months and overall survival by 6.6 months.[72] In a large, randomized study, combination therapy with melphalan, prednisone, and bortezomib significantly increased the rate of complete response, the time to progression, and overall survival, as compared with melphalan and prednisone alone.[73,74] Combination therapy with melphalan and prednisone plus either thalidomide or bortezomib is now considered the standard of care for patients who are not eligible for transplantation. In studies of combination therapies that included glucocorticoids plus thalidomide or bortezomib and in which cyclophosphamide was substituted for melphalan to reduce hematologic toxic effects, response rates were unchanged, but outcome data were not reported.[43,56] In a randomized study, combination therapy with melphalan, prednisone, and lenalidomide, followed by lenalidomide maintenance therapy, was superior to therapy with melphalan and prednisone alone. The complete response rate was higher with the three-drug combination, and progression-free survival was improved by lenalidomide maintenance therapy, but no survival differences were noted. Among patients between the ages of 65 and 75 years, combination therapy with melphalan, prednisone, and lenalidomide without lenalidomide maintenance therapy improved progression-free survival, as compared with therapy with melphalan and prednisone alone, although no differences were seen in patients older than 75 years of age.[47]

Another combination therapy, lenalidomide plus dexamethasone, increased the complete response rate and progression-free survival, as compared with high-dose dexamethasone alone.[75] In a randomized study comparing lenalidomide plus either low-dose or high-dose dexamethasone, the use of low-dose dexamethasone improved survival and reduced the frequency of serious adverse events.[54] Thus, lenalidomide plus low-dose dexamethasone is an alternative to previous regimens. Ongoing randomized studies of this treatment, as compared with combination therapy with melphalan, prednisone, and thalidomide, should provide data on the relative efficacy and safety profile of these therapies. A more intensive approach, a four-drug combination of bortezomib, melphalan, prednisone, and thalidomide, followed by maintenance therapy with bortezomib and thalidomide, has had unprecedented success in elderly patients, with a 3-year progression-free survival rate of 56%. To further optimize treatment, the dosing schedule for bortezomib was reduced from twice- to once-weekly infusions. The once-weekly schedule of bortezomib did not significantly affect progression-free survival but considerably reduced the risk of peripheral neuropathy.[76,77]

CONSOLIDATION AND MAINTENANCE THERAPIES

Consolidation therapy (two to four cycles of combination therapies after induction treatment) and maintenance therapy (continuous therapy with single agents until the time of disease progression) are widely accepted, although no specific guidelines are available. Consolidation with four courses of combination therapy with bortezomib, thalidomide, and dexamethasone after autologous transplantation has been reported to increase the complete-response rate from 15% to 49%.[36] Several randomized studies have explored the role of thalidomide maintenance therapy after autologous transplantation or conventional treatments. There was improvement in the rate of progression-free survival, though a survival benefit was not always evident. However, the risk of peripheral neuropathy after long-term thalidomide exposure limits its routine use.[40-44] Lenalidomide may offer the same benefits with fewer toxic effects, and few cases of second cancers have been reported. In two independent, randomized studies involving patients who had undergone autologous transplantation, lenalidomide maintenance therapy decreased the risk of progression by 54% and 58% in comparison with no maintenance therapy.[45,46] In elderly patients who received combination therapy with melphalan, prednisone, and lenalidomide, lenalidomide maintenance therapy reduced the risk of progression by 75% in comparison with the risk among control subjects.[47] This benefit was evident in all categories of patients and was independent of the quality of response achieved after induction. Although the role of bortezomib plus an immunomodulatory drug in maintenance therapy remains to be elucidated, the results from two independent trials support this type of approach in elderly patients.[76,77] At present, lenalidomide appears to be the most suitable choice for maintenance, whereas bortezomib is under evaluation in randomized studies.[55,57] To date, no data are available to assess the potential risk of refractory relapse after maintenance therapy.

THERAPY AT RELAPSE

In treating patients with relapsed or refractory myeloma, the quality and duration of the response to previous therapy are the most important prognostic factors. A complete response to previous therapy may warrant repeating the treatment for subsequent relapses. Patients with newly diagnosed disease who have a relapse after 2 years retreated or patients with relapsed or refractory myeloma whose disease recurs after 1 year of remission may be retreated with the same therapy. In contrast, patients with recurrent disease after a shorter period of time should receive a different treatment.[78] Combination therapy with dexamethasone and either bortezomib[79,80] or lenalidomide[81,82] is the treatment of choice for patients with relapsed or refractory myeloma. Retrospective analyses indicate that these agents are associated with a superior outcome when given at first relapse than when given later.[79,83] Autologous transplantation is an option for patients who did not undergo transplantation at diagnosis, as well as for those who underwent transplantation and had a prolonged duration of remission.[84]

In a randomized study, treatment with bortezomib and liposomal doxorubicin was superior to bortezomib alone.[85] That study showed the in vivo additive or synergistic effects of combinations including bortezomib and chemotherapy. The efficacy of bortezomib or lenalidomide plus dexamethasone appeared to be enhanced by the addition of a third agent, such as cyclophosphamide, melphalan, or doxorubicin, which suggested that such combination therapy might be used more in clinical practice when established salvage regimens have been exhausted or the disease is resistant to therapy.[33,86] The combination of lenalidomide, bortezomib, and dexamethasone can achieve a response even when the disease is resistant to thalidomide, lenalidomide, or bortezomib. Thalidomide plus dexamethasone is an effective salvage treatment, does not induce cytopenia, and appears to be a valuable option in advanced stages of disease or in frail patients when hematologic toxic effects are a concern.[78]

SUPPORTIVE THERAPY

Erythropoiesis-stimulating agents are recommended during treatment to reduce anemia when no increase in the hemoglobin level is evident despite a tumor response to treatment.[87] Bone pain requires systemic analgesia, local measures, and chemotherapy. Treatment of pain should start with nonopioid analgesic agents (e.g., paracetamol); nonsteroidal antiinflammatory drugs should be avoided because of the potential risk of renal damage. Opioid analgesic agents should be introduced when nonopioid analgesic agents are ineffective. Initial therapy should include weak opioids (codeine), with stronger opioids (mor-

phine or oxycodone) reserved for patients with an inadequate response.[88]

Local radiotherapy is effective for palliation of bone pain, with fractionated radiotherapy relieving pain in 91 to 97% of patients.[89] Pathologic fractures usually require surgical stabilization. Percutaneous vertebroplasty, which is an option in patients with vertebral collapse, ameliorates pain but does not restore vertebral height.[90] The use of bisphosphonates can reduce new bone lesions and pathologic fractures. Bisphosphonate therapy should be continued only for 2 years to limit the possibility of osteonecrosis of the jaw, and concomitant calcium and vitamin D_3 treatment should be considered to prevent electrolytic imbalance.[91] The survival benefit has recently been reported in patients with newly diagnosed disease who received zoledronic acid.[92] A comprehensive dental examination before bisphosphonate therapy, maintenance of good oral hygiene, and avoidance of invasive oral procedures can reduce the risk of osteonecrosis of the jaw.[93]

In patients with renal insufficiency, further deterioration of renal function[22] and the development of the tumor lysis syndrome can be prevented with the use of appropriate hydration, urine alkalinization, rapidly acting therapy for myeloma, and treatment of hypercalcemia, hyperuricemia, and infections. Hypercalcemia requires immediate treatment with adequate hydration, diuretics, glucocorticoids, and bisphosphonates.[94] Prophylaxis with trimethoprim–sulfamethoxazole should be considered during the first 3 months of chemotherapy or after transplantation, when the risk of infection is increased. Acyclovir prophylaxis is recommended for all patients receiving bortezomib-based therapies.[23] Although the benefit of vaccination remains controversial, vaccination to prevent *Haemophilus influenzae* should be considered. However, vaccinations against *Streptococcus pneumoniae* and influenza virus have not been effective. The use of intravenous immune globulin is reserved for patients with recurrent life-threatening infections or very low IgG levels.

MANAGEMENT OF ADVERSE EVENTS RELATED TO THERAPY

Hematologic toxic effects are quite frequent when thalidomide, lenalidomide, or bortezomib is used together with conventional chemotherapy but are less frequent when these drugs are used with dexamethasone alone. Granulocyte colony-stimulating factor can decrease the incidence of neutropenia. Chemotherapy should be withheld when the neutrophil count is less than 500 cells per cubic millimeter despite the use of granulocyte colony-stimulating factor and then restarted with an appropriate dose reduction when the neutrophil count recovers to at least 1000 cells per cubic millimeter. Similarly, therapy should be interrupted when the platelet count is under 25,000 cells per cubic millimeter and restarted when it rises to 50,000 cells per cubic millimeter after appropriate dose reduction of the implicated drug.[95]

Among patients with newly diagnosed disease, the incidence of both venous and arterial thrombosis rises when either thalidomide[52,66-71] or lenalidomide[54,75] is combined with dexamethasone or chemotherapy; thromboprophylaxis is required for the first 6 months of therapy. Low-dose aspirin is indicated for patients at standard risk for thromboembolic events; either low-molecular-weight heparin or full-dose warfarin is preferred in high-risk patients (i.e., those who are obese, are immobilized, have a central venous catheter, or have a history of thromboembolism, cardiac disease, chronic renal disease, diabetes, infections, or surgical procedures). Therapy should be suspended in patients who have a thromboembolic event during treatment and should be restarted after improvement or resolution.[96] The risk of venous thromboembolism is not increased with the use of bortezomib.[97]

Bortezomib and thalidomide can cause peripheral neuropathy[66-71,73,76,79]; lenalidomide is rarely associated with severe neuropathy.[47,54,81,82] Both thalidomide- and bortezomib-related neuropathies are cumulative and dose-dependent. Patients should be taught to recognize peripheral neuropathy; early dose reduction of the suspected drug is the most effective way to treat this condition. Mild, uncomplicated paresthesia requires only dose reduction. Treatment should be discontinued when severe paresthesias or pain or sensory loss interfering with activities of routine daily life occur and then reinitiated at lower doses when symptoms abate. Halving the dose is usually required, and twice-weekly bortezomib should be reduced to weekly infusion.[76,95,98] Gabapentin and pregabalin can relieve neuropathic symptoms.

In patients over 75 years of age or in younger patients with heart, lung, liver, or renal dysfunc-

tion, lower doses of standard regimens may prevent toxic effects requiring treatment discontinuation (Table 3). Age-adjusted dose reductions are recommended: dexamethasone should be reduced from 40 to 20 mg weekly,[31,54] melphalan from 0.25 to 0.18 or 0.13 mg per kilogram of body weight on days 1 to 4,[47,66-71,73] lenalidomide from 25 to 15 mg on days 1 to 21,[95] thalidomide from 200 to 100 or 50 mg per day,[66-71] and bortezomib (at a dose of 1.3 mg per square meter) from twice- to once-weekly infusion.[76]

FUTURE DIRECTIONS

Ongoing studies are incorporating thalidomide, lenalidomide, or bortezomib in treatment approaches to further improve outcomes by defining combinations associated with maximal tumor reduction, evaluating consolidation or maintenance therapies that delay tumor regrowth, and determining which regimens provide a benefit with favorable side-effect profiles in specific subgroups of patients. Efforts are under way to develop risk-adapted strategies in which therapies may be based on knowledge of genetic polymorphisms or mutations that modulate molecular pathways that underlie disease pathogenesis.[99] New proteasome inhibitors (carfilzomib), immunomodulatory drugs (pomalidomide), targeted therapies (inhibitors of NF-κB, MAPK, and AKT), epigenetics agents (histone deacetylase inhibitors vorinostat and panobinostat), and humanized monoclonal antibodies (elotuzumab and siltuximab) are currently being investigated in clinical trials.[100]

CONCLUSIONS

In Western countries, the frequency of myeloma is likely to increase in the near future as the population ages. The recent introduction of thalidomide, lenalidomide, and bortezomib has changed the treatment paradigm and prolonged survival of patients with myeloma. At diagnosis, regi-

Table 3. Suggested Age-Adjusted Dose Reduction in Patients with Multiple Myeloma.

Drug	Age <65 Yr	Age 65–75 Yr	Age >75 Yr
Dexamethasone	Dose of 40 mg/day given orally on days 1–4, 15–18 every 4 wk; or 40 mg/day given orally on days 1, 8, 15, 22 every 4 wk[54]	Dose of 40 mg/day given orally on days 1, 8, 15, 22 every 4 wk[54]	Dose of 20 mg/day given orally on days 1, 8, 15, 22 every 4 wk[95]
Melphalan	Dose of 0.25 mg/kg given orally on days 1–4 every 6 wk[67]	Dose of 0.25 mg/kg given orally on days 1–4 every 6 wk[67]; or 0.18 mg/kg given orally on days 1–4 every 4 wk[47]	Dose of 0.18 mg/kg given orally on days 1–4 every 6 wk; or 0.13 mg/kg given orally on days 1–4 every 4 wk
Cyclophosphamide	Dose of 300 mg/m^2 given orally on days 1, 8, 15, 22 every 4 wk[56]	Dose of 300 mg/m^2 given orally on days 1, 8, 15, every 4 wk[43]; or 50 mg/day given orally on days 1–21 every 4 wk	Dose of 50 mg/day given orally on days 1–21 every 4 wk; or 50 mg every other day given orally on days 1–21 every 4 wk
Thalidomide	Dose of 200 mg/day given orally continuously[67,69]	Dose of 100 mg/day[66] or 200 mg/day[67,69] given orally continuously	Dose of 50 mg/day[43] to 100 mg/day[66,70] given orally continuously
Lenalidomide	Dose of 25 mg/day given orally on days 1–21 every 4 wk[54,81,82]	Dose of 15–25 mg/day given orally on days 1–21 every 4 wk[54,81,82]	Dose of 10–25 mg/day given orally on days 1–21 every 4 wk[54,81,82]
Bortezomib	Dose of 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk[73,79]	Dose of 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk[73,79]; or 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 8, 15, 22 every 5 wk[76]	Dose of 1.0–1.3 mg/m^2 given as bolus intravenous infusion on days 1, 8, 15, 22 every 5 wk[76]

mens that are based on bortezomib or lenalidomide, followed by autologous transplantation, are recommended in transplantation-eligible patients. Combination therapy with melphalan and prednisone plus either thalidomide or bortezomib is suggested in patients who are not eligible for transplantation. Maintenance therapy with thalidomide or lenalidomide improves progression-free survival, but longer follow-up is needed to assess the effect on overall survival. At relapse, combination therapies with dexamethasone plus bortezomib, lenalidomide, or thalidomide or with bortezomib plus liposomal doxorubicin are widely used. In the case of cost restrictions, combinations including glucocorticoids, alkylating agents, or thalidomide should be the minimal requirement for treatment.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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