Multiple Myeloma: Charging Toward a Bright Future

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ABSTRACT Multiple myeloma (MM) is an incurable clonal B-cell malignancy with terminally differentiated plasma cells. It afflicts approximately 55,000 people in the United States. Over the past 5 years, significant progress has been made in the diagnosis and assessment of patients with MM. Significant advances include a simplified staging system, which has replaced the more cumbersome Durie-Salmon staging system; an updated uniform international response criteria; the development of a sensitive new serum test to detect free light chain production (free light chain assay); the recognition of specific adverse cytogenetic abnormalities; and the evolution of genomics, which will identify specific and targeted therapies for individual MM patients. For the first time in decades, major therapeutic advances have been implemented in the treatment of MM patients. These include 2 new classes of agent: immunomodulatory drugs and proteosome inhibitors. In addition, clinical trials have solidified the role of hematopoietic stem cell transplant and established the benefits of post-transplant maintenance therapy. Finally, a number of new agents are in development that specifically target the myeloma cells and/or the bone marrow microenvironment. These advances have resulted in expanded treatment options, prolonged disease control and survival, and improved quality of life for patients with MM. (CA Cancer J Clin 2007;57:301–318. © American Cancer Society, Inc., 2007.

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EPIDEMIOLOGY

Multiple myeloma (MM) accounts for 1% of all malignancies: 10% of all hematological malignancies in Caucasians and 20% in African Americans. It is the second most common hematologic malignancy in the United States. The overall incidence rate in the United States is 4.4/100,000/year with a male:female ratio of 1.4:1. The reason for the higher incidence in men and African Americans is not known. The American Cancer Society (ACS) estimates that about 19,900 new cases of MM (10,960 in men and 8,940 in women) will be diagnosed during 2007, and about 10,790 are expected to die of the disease. Internationally, MM accounts for 0.8% of all cancer deaths with approximately 86,000 new cases per year. The current 5-year survival for a patient newly diagnosed with MM in the United States was 33% (data from 1996 to 2002), up from 26% 30 years ago. In patients treated on clinical trials, the median survival is approximately 50%.

DISEASE CHARACTERISTICS

Multiple myeloma is a B-cell malignancy with terminally differentiated plasma cell phenotype. The characteristic findings in MM are lytic bone disease, renal insufficiency, anemia, hypercalcemia, and immunodeficiency. The most common presenting symptoms are fatigue, bone pain, and recurrent infections. Any of these findings should alert the clinician to the possibility of MM and warrant further clinical investigation. In newly diagnosed patients, skeletal abnormalities are present on conventional radiography in approximately 60% to 80% of patients, anemia is present in 70% of patients, hypercalcemia in 15%, and elevated serum creatinine in 20%. However, approximately 25% of patients present without symptoms and are identified incidentally by laboratory results, such as an elevated total protein, encountered during routine testing or in evaluation of other health problems.
Plasma cell dyscrasias can be divided into premalignant and malignant conditions. Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition, whereas asymptomatic MM and active MM are malignant. Asymptomatic MM is differentiated from active myeloma by end-organ compromise designated by the acronym “CRAB” (hypercalcemia, renal insufficiency, anemia, or bone lesions)(Table 1).7

MGUS is a premalignant condition that may progress to MM. MGUS has been found in 3.2% of persons aged 50 years or older and 5.3% of persons aged 70 years or older in the United States.8 MGUS is approximately 80 to 100 times more common than MM. Whereas the rate of progression of MGUS to MM is 1% per year, approximately three fourths of these individuals remain without conversion to 20 or more years.9 Similar cytogenetic abnormalities (translocations and deletions) reported in MM have been observed in patients with MGUS. However, no obvious clinical or biologic correlations are associated with these chromosome abnormalities.10

As we better understand the molecular evolution of disease, additional markers may better differentiate MGUS from MM.11

MGUS is defined by a monoclonal immunoglobulin concentration in serum of ≤3 g/dL, the absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency, and a bone marrow with ≤10% plasma cells.7,12 (Table 1). Recently, it has been established that MGUS patients can be stratified to high or low risk as defined by their immunoglobulin isotype, the level of their paraprotein secretion, and the ratio of serum free light chains. For example, a patient with a monoclonal immunoglobulin other than immunoglobulin G (IgG), serum monoclonal immunoglobulin concentration ≥1.5 g/dL, and an abnormal serum free light chain ratio would be classified as high risk with 58% risk of progression of MGUS to MM at 20 years compared with 5% if none of these factors are present (Table 2).13 After initial consultation with a specialist to establish the diagnosis of MGUS, patients with low-risk MGUS can be followed yearly with blood and urine studies by their primary care physicians. High-risk MGUS patients should be followed every 3 to 6 months by a specialist to evaluate for progression to myeloma.

### LABORATORY EVALUATION (TABLE 3)

The standard evaluation of a patient with suspected plasma cell dyscrasia includes the following:
- Complete blood count with differential;
• Blood chemistry profile including calcium, creatinine, lactate dehydrogenase (LDH), and albumin;

• Bone marrow aspirate and biopsy for routine histology and immunohistochemistry, metaphase cytogenetics, fluorescent in situ hybridization (FISH) for plasma cell dyscrasia markers (immunoglobulin heavy chain gene translocation; chromosome 1, 13, and 17 abnormalities), and flow cytometry for B-cell markers;

• Complete skeletal survey (For patients with localized symptoms not explained by plain films, MRI should be performed. PET/CT are not uniformly recommended at this time.);

• Serum and urine electrophoresis with immunofixation to identify the M protein and quantification of this protein (Urine sample should be a 24-hour urine collection.);

• Serum β-2 microglobulin;

• Serum free light chain assay with κ/λ ratio

(The serum free light chain assay can identify monoclonal paraproteins in over 98% of patients.).

Serum protein electrophoresis (SPEP) with immunofixation shows a monoclonal spike in 93% of MM patients.6 Urine electrophoresis shows a monoclonal spike in 75% of MM patients. Sixty percent of the patients have a monoclonal protein that is IgG, 20% IgA, 1% IgD or nonsecretory, and 15% are light chain only.

Up to 2% of patients diagnosed with MM have no detectable M protein (ie, not present in the serum or the urine by protein electrophoresis). In these patients, the serum free light chain assay, which measures the level of free (unbound) κ and λ light chains in the serum, may help confirm the diagnosis of MM.14 The serum free light chain assay can identify monoclonal paraproteins in over 70% of patients previously thought to have nonsecretory disease. The serum free light chain assay is the test of choice for oligosecretory myeloma (serum M spike <1 g/dL, urine M spike <200 mg/24 hours) and for a related plasma

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**TABLE 2** Risk-stratification Model to Predict Progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders

| Risk Group                              | Relative Risk | Absolute Risk of Progression at 20 Years | Absolute Risk of Progression at 20 Years Accounting for Death as a Competing Risk |
|-----------------------------------------|---------------|------------------------------------------|---------------------------------------------------------------------------------|
| Low risk: serum M protein <1.5 g/dL, IgG subtype, normal FLC ratio (0.26 to 1.65) | 1             | 5%                                       | 2%                                                                              |
| Low-intermediate risk: any 1 factor abnormal | 5.4           | 21%                                      | 10%                                                                             |
| High-intermediate risk: any 2 factors abnormal | 10.1          | 37%                                      | 18%                                                                             |
| High risk: all 3 factors abnormal       | 20.8          | 58%                                      | 27%                                                                             |

FLC = free light chain.

Modified from Rajkumar SV, Kyle RA, Therneau TM, et al13 with permission from Blood.

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**TABLE 3** Initial Workup for Multiple Myeloma

- History and physical examination
- Complete blood count and differential
- Chemistry profile including albumin, calcium, and creatinine
- Quantitative immunoglobulins
- Serum free light chain assay
- Serum protein electrophoresis, immunofixation electrophoresis
- 24-hour urine collection for total urine protein, electrophoresis, and immunofixation
- Bone marrow aspirate and trephine biopsy (immunohistochemistry, cytogenetics, FISH, flow cytometry) (plasma cell labeling index, if available)
- Radiological skeletal bone survey including spine, pelvis, skull, humeri, and femurs; MRI may be helpful in select cases
- Serum β-2 microglobulin, C-reactive protein, and lactate dehydrogenase

FISH = fluorescent in situ hybridization.
cell dyscrasia, primary systemic amyloidosis. In addition, the serum free light chain assay is a very sensitive marker for disease response and progression.

**PROGNOSIS**

A new staging system for MM, the International Staging System (ISS) (Table 4), has replaced the Durie–Salmon staging system (Table 5) in clinical practice. The 2 key advantages of the ISS are ease of use and more accurate prognostic information. There are only 2 variables assessed when determining a patient's stage according to the ISS: serum albumin and $\beta_2$ microglobulin ($\beta_2$M) that can be evaluated at virtually any clinical laboratory. Using these 2 variables, the clinician can correlate the patient's stage with median survival (Table 4).

The basis for the ISS was an analysis of data from 10,750 MM patients in Europe, North America, and Asia from 1981 to 2002. A combination of $\beta_2$M and serum albumin provided the simplest, most powerful, reproducible 3-stage classification. The ISS was validated in the remaining patients and shown to correlate with survival, as well as with the previous benchmark, the Durie–Salmon staging system.

As our understanding of the biology of MM has increased, additional prognostic factors have been identified. This information, not yet included in the ISS, may identify patients with high-risk MM in whom conventional therapy may be less effective with shorter life expectancy. Some of the high-risk findings are listed in Table 6. Additional reported high-risk factors include elevated LDH and amplifications of the chromosome 1q21 region.

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**TABLE 4 International Staging System and Median Survival**

| Stage | Criteria | Median Survival (Months) |
|-------|----------|--------------------------|
| I     | Serum $\beta_2$ microglobulin <3.5 mg/L and serum albumin >3.5 g/dL | 62 |
| II    | Not stage I or III* | 44 |
| III   | Serum $\beta_2$ microglobulin >5.5 mg/L | 29 |

*There are 2 categories for Stage II: serum $\beta_2$ microglobulin <3.5 mg/L, but serum albumin <3.5 g/dL; or serum $\beta_2$ microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level.

**TABLE 5 Durie-Salmon Staging System, Assessment of Tumor Mass, Older Staging System for Myeloma**

| Stage I: Low Tumor Mass (<0.6 x 10^{12} Myeloma Cells/m^2) |
|-----------------------------------------------------------|
| All of the following must be present:                     |
| Hemoglobin >10.5 g/dl or hematocrit >32 volume %          |
| Serum calcium normal                                      |
| Low myeloma protein production                            |
| IgG peak <5 g/dl                                          |
| IgA peak <3 g/dl                                          |
| Bence Jones protein <4 g/24 hour                          |
| No bone lesions                                           |

| Stage II: Intermediate Tumor Mass (0.6 to 1.2 x 10^{12} Myeloma Cells/m^2) |
|----------------------------------------------------------------------------|
| Fitting neither Stage I nor Stage III                                   |

| Stage III: High Tumor Mass (>1.2 x 10^{12} Myeloma Cells/m^2) |
|----------------------------------------------------------------|
| One or more of the following abnormalities must be present:     |
| Hemoglobin <8.5 g/dl                                           |
| Serum calcium >12 mg/dl                                       |
| Very high myeloma protein production                          |
| IgG peak >7 g/dl                                              |
| IgA peak >5 g/dl                                              |
| Bence Jones protein >12 g/24 hour                            |
| >3 lytic lesions on bone survey (bone scan not acceptable)    |
Gene expression profiling (GEP) is a new technology that can assay thousands of genes for individual patients. Preliminary GEP studies have also demonstrated that individual genes (eg, CSK1-B) or groups of genes can define prognosis with greater accuracy than conventional genetic markers and can provide pharmacogenomic and biologic insight into the pathophysiology, therapeutics, and future targets of myeloma. For example, using a 70-gene model, the Arkansas group reported that altered transcriptional regulation of genes mapping to chromosome 1 may contribute to disease progression and that expression profiling can be used to identify high-risk disease and guide therapeutic interventions. A recent prognostic model evaluating 5 different variables demonstrated that GEP was the strongest predictor of outcome.

Multiple myeloma is characterized by genomic alterations frequently involving gains and losses of chromosomes. Another evolving technology involves single nucleotide polymorphism (SNP)-based mapping arrays, which allow the identification of gene-copy number changes and loss of heterozygosity. Preliminary studies have shown that SNP analysis can predict for response, toxicities, and survival. In addition, a recently proposed prognostic system based on cyclin D expression in myeloma cells has been predictive of response to treatment and survival.

### TABLE 6 Criteria for High-risk Multiple Myeloma*

| High-risk Abnormality | Percentage of Patients with Newly Diagnosed Multiple Myeloma with Abnormality |
|-----------------------|------------------------------------------------------------------------------|
| Cytogenetics          |                                                                              |
| Deletion of chromosome 13 | 14                                                                            |
| Hypoploidy            | 9                                                                             |
| Either hypoploidy or deletion of chromosome 13 | 17                                                                            |
| Fluorescence in situ hybridization (FISH) |                                                                              |
| t(4;14)                | 15                                                                            |
| t(14;16)               | 5                                                                             |
| 17p−                   | 10                                                                            |
| Plasma cell labeling index >3% | 6 |
| Any 1 of the high-risk abnormalities | 25–30                                                                        |

*Elevated lactate dehydrogenase and additions of chromosome 1q have also been reported as high-risk factors. Modified from Stewart AK, Bergsagel PL, Greipp PR, et al17 with permission from Leukemia.

### TREATMENT

#### Conventional Therapies

The number of therapeutic options in the treatment of MM has increased dramatically since the beginning of the millennium, and prospects for the future are even more encouraging. From the 1960s until very recently, conventional therapy for patients with MM was glucocorticoid-based in combination with alkylating agents and/or anthracyclines. Melphalan plus prednisone (MP) has been one of the gold standards for treatment for the last 40 years. Cumulative exposure to melphalan, however, is associated with an increased risk of marrow toxicity, including myelodysplasia, acute leukemia, and impaired stem cell production. This is an important consideration in patients who are candidates for high-dose therapy with stem cell rescue (autologous transplants). Variations of the MP regimen (eg, vincristine, BCNU, melphalan, cyclophosphamide, prednisone) have not proven to be superior. With conventional therapy, approximately 5% of patients achieve complete remission (CR). Salvage therapy for relapsed or primary refractory disease initially utilized the vincristine plus doxorubicin plus dexamethasone (VAD) regimen. This produced response rates of 40% to 50% in relapsed disease and about 30% in patients with primary refractory disease. The most active agent in the combination is dexamethasone. High-dose dexamethasone pulsing alone induces...
responses in about 30% to 50% of patients, regardless of prior response.28

**Novel Therapies**

With the incorporation of new classes of medications in the treatment of MM, the old treatment paradigm has shifted, but not excluded conventional approaches. The effectiveness of the immunomodulatory agents thalidomide and lenalidamide, as well as bortezomib, a proteasome inhibitor, has greatly expanded treatment options. These agents, alone or in combination, increase response rates and durability of responses, translating into improved survival.

**Thalidomide (Thalomid®)**

The precise mode of action of thalidomide is unknown. Proposed mechanisms of action include angiogenesis inhibition, possibly by downregulation of vascular endothelial growth factor (VEGF); immune modulation by increasing natural killer cell activity, interleukin-2, and gamma interferon; and increasing apoptosis. It is reasonably well tolerated; the toxicities include increased risk for venous thromboembolism (DVT), rash, bradycardia, syncope, hypothyroidism, somnolence, constipation, and peripheral neuropathy.

The effectiveness of thalidomide in MM was first reported in relapsed/refractory MM by the Arkansas group in 1999.29 Subsequently, its efficacy in front-line therapy has been demonstrated in randomized clinical trials (RCTs). The Eastern Cooperative Oncology Group (ECOG) reported a superior response rate to a combination of thalidomide plus dexamethasone compared with dexamethasone alone (63% versus 41%, respectively; P = 0.01).30 Preliminary results of an international study with a comparable design found similar response rates (63% versus 40%).31 In addition, the median time to progression was superior in the thalidomide arm (22.4 months versus 6.5 months, respectively).31

An Italian study combined thalidomide with the old “gold standard”—melphalan and prednisone (MPT)—in elderly patients. MPT demonstrated a superior response rate (76% versus 48%, respectively), 2-year event-free survival (54% versus 27%, respectively), and 3-year survival (80% versus 64%, respectively) compared with MP alone.32 A 3-arm trial from France compared MP, MPT, and melphalan 100mg/m² (intermediate dose) with autologous stem cell support.33 They reported a superior response rate, duration of response, and survival in the MPT arm.

In each of these studies, the DVT rate was increased in the group treated with thalidomide. Subsequent reports indicate that the risk of DVT with either of these immunomodulatory agents (thalidomide or lenalidomide) is directly related to the dose of concomitant corticosteroids and the use of erythropoietic agents. Whereas immunomodulatory agents have proven efficacy in MM, prophylaxis against DVTs must be considered, especially when combined with high-dose steroids and erythropoietins.34

**Lenalidomide (Revlimid®)**

Lenalidomide is an analog of thalidomide. It is generally better tolerated than thalidomide. The most common side effect is myelosuppression that is usually reversible. The effectiveness of lenalidomide has been demonstrated in 2 parallel Phase III clinical trials: patients with relapsed/refractory MM were randomized to lenalidomide plus dexamethasone or dexamethasone alone.35 In both studies, the patients in the lenalidomide group had superior response rates and duration of response (11 months versus 5 months, respectively; P < 0.001). Side effects were manageable, with approximately 20% of the patients withdrawn from the study due to toxicities. However, since the Phase II and III clinical trials restricted patient eligibility to creatinine levels ≤2.5 mg/dL, and as lenalidomide is predominantly renally excreted, one should use lenalidomide with caution in patients with creatinine levels >2.5 mg/dL.36

A pilot trial of lenalidomide plus dexamethasone as induction therapy demonstrated impressive response rates (91%) with minimal toxicities.37 To reduce the toxicities associated with high-dose dexamethasone, a recently completed ECOG Phase III trial compared lenalidomide with either standard (480 mg/month) or low-dose (160 mg/month) dexamethasone. Preliminary analysis revealed significantly less toxicity,
including deaths, in the low dexamethasone cohort.\textsuperscript{38} Response criteria are not yet available from this study.

**Bortezomib (Velcade\textsuperscript{\textregistered})**

The proteosome inhibitor bortezomib is another recent addition to the MM treatment armamentarium. The target of bortezomib is the 26S proteosome. This large, multisubunit protein complex is present in high amounts in both the cytoplasm and nucleus of all eukaryotic cells. It functions to degrade cellular proteins that have been “tagged” by the cell for destruction.\textsuperscript{39} When the proteosome is turned off by a small molecule such as bortezomib, the “tagged” proteins may accumulate. Those same proteins serve critical functions, such as regulation of the cell cycle, transcription, and apoptosis, as well as the regulation of chemotaxis, angiogenesis, and cell adhesion, well characterized in the NF-κB pathway.\textsuperscript{40} Thus, the proteosome is an essential component of cellular metabolism and regulation.

Bortezomib received fast-track approval for refractory MM in 2003. The benefit of bortezomib was further shown in the Phase III APEX trial.\textsuperscript{41} Patients with relapsed/refractory MM were randomized to receive bortezomib or dexamethasone. The response rate, median time to progression, and 1-year survival were significantly increased in the bortezomib group. The most common adverse effects of bortezomib include peripheral neuropathy, transient thrombocytopenia, and gastrointestinal disorders (nausea, diarrhea, and constipation).

**Combination Therapy**

Combination regimens consisting of conventional agents with newer agents like thalidomide, lenalidomide, and bortezomib are actively under investigation. The decision regarding which agent(s) to employ in a patient with newly diagnosed MM remains hotly debated. Currently, only thalidomide is Food and Drug Administration-approved as front-line therapy. However, pilot trials with lenalidomide or bortezomib as front-line treatment have reported higher overall and complete response rates than those observed with thalidomide-based regimens. Although high complete response rates have been observed with the novel agents, the duration of these responses has not been determined. Furthermore, novel combination induction regimens have not been compared with autologous transplant in clinical trials. Therefore, a rational approach to choosing an initial regimen depends on whether or not the patient is a candidate for autologous stem cell transplantation (ASCT).

In newly diagnosed patients who are candidates for transplantation, alkylating agents, particularly melphalan, may compromise the
effectiveness of stem cell harvesting and should be avoided.42 

One proposed algorithm for treating patients with newly diagnosed MM is shown in Figure 1.43 Unfortunately, high-risk patients do not have comparable survival with standard-risk patients following autologous transplants. These patients should be considered for novel treatment approaches that may include transplantation. Patients who are not candidates for transplantation (Figure 2) can begin therapy with standard alkylating agent therapy. Indeed, based on the French and Italian studies, MPT is accepted as one of the standard treatments for nontransplant-eligible patients.

**Maintenance Therapy Following Conventional Therapy**

Until the mid-1990s, interferon α was considered the standard maintenance therapy following conventional therapy and high-dose therapy with ASCT. However, a meta-analysis of over 4,000 patients enrolled on clinical trials showed minimal impact on survival.44 More recently, 2 randomized trials showed the benefit of corticosteroid maintenance therapy following conventional induction therapy. Prednisone 50 mg administered every other day resulted in an improvement in both progression-free (14 versus 5 months) and overall survival (37 versus 26 months) in VAD chemotherapy responsive patients.45 Another trial comparing dexamethasone maintenance with observation demonstrated an improvement in progression-free survival in the dexamethasone arm (2.8 years versus 2.1 years).46

**Hematopoietic Stem Cell Transplant (HSCT) in MM**

**Autologous**

Single Autologous Transplantation. ASCT provides the best opportunity for most patients to achieve a complete response and to prolong event-free survival. Initially introduced to help overcome the native resistance of myeloma cells to conventional chemotherapy, high-dose therapy requiring autologous hematopoietic stem cell support was first evaluated in patients with refractory disease.47 This resulted in improved response rates and overall survival. This approach was then extended to newly diagnosed patients. In 1996, the seminal randomized study on symptomatic Stage II and III patients by the French Myeloma Intergroup showed conclusively that high-dose therapy yielded a superior disease-free and overall survival outcome compared with conventional therapy.48 The 5-year projected survival for the transplant group was 52% versus 12% for the conventional therapy group. Whereas complete responses were observed in only 5% of the conventional therapy group, 22% of the high-dose therapy group achieved CRs. The transplant-related mortality (TRM) was only 2.7%. Other randomized and nonrandomized comparisons have also demonstrated that high-dose therapy is superior to conventional chemotherapy.49–51 In the Arkansas study, patients achieving complete response had a median disease-free survival of 50 months and a median overall survival of more than 7 years.50 In the era before novel agents, the incorporation of high-dose therapy with autologous transplant into the treatment algorithm resulted in marked improvement in the

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**FIGURE 2** Nonstudy treatment algorithm for transplantation-eligible patients with newly diagnosed active myeloma. Separating treatment by risk as shown in this algorithm has not yet been supported by clinical trials; level of evidence is clearly indicated in the text. CR indicates complete remission; MPT, melphalan, prednisone, and thalidomide. Reproduced from Dispenzieri A, Rajkumar SV, Gertz MA, et al43 with permission from Mayo Clinic Proceedings.
median survival for newly diagnosed patients compared with conventional therapies.

One issue raised was the optimal timing of the transplant. Two randomized studies comparing early versus late transplant at relapse showed comparable overall survival.5,52 In the French study, they reported higher quality-of-life scores in the upfront transplant cohort, suggesting a valid benefit for upfront ASCT.52 Therefore, high-dose therapy with ASCT has been well established as appropriate care for front-line therapy in many newly diagnosed MM patients, particularly those younger than age 70 years. This should include patients with primary refractory disease who also benefit from autologous transplantation.53,54 Multiple myeloma is currently the most common indication for ASCT in North America, with over 5,000 transplants performed yearly (Center for International Blood and Marrow Transplant Research [CIBMTR] estimates). Indeed, national and international guidelines now recommend the adoption of upfront ASCT in transplant-eligible patients with newly diagnosed MM.43

High-dose therapy with autologous transplant for patients with disease relapse has not been evaluated in randomized or pair-matched case controls. In previously treated patients with chemotherapy-sensitive relapse, 75% of transplanted patients achieved 75% tumor reduction, including true complete responses of 10% to 15%.55 The median relapse-free survival and overall survival is on the order of 2 and 3 years, respectively. In patients with refractory relapse, high-dose therapy with ASCT resulted in a median event-free survival and overall survival of 11 and 19 months, respectively.56

Tandem Autologous Transplantation. Sequential planned tandem ASCT was developed in an attempt to increase dose intensity and achieve deeper sustained remissions. Reported CR rates with single ASCT have been in the 25% to 35% range, whereas tandem autologous transplantation has an expected CR rate ranging from 35% to 50%. The Arkansas group pioneered tandem ASCT and observed an impressive event-free and overall survival duration of 43 months and 68 months, respectively—superior to historical controls.50 In a recent update of the original cohort of 231 patients, 33% of the patients were alive at 10 years and 17% at 15 years, with 15% and 7%, respectively, in continuous remission.57 More recently, the Arkansas group has incorporated thalidomide into a tandem transplant approach and showed superior 5-year continuous CRs (60%) and improved event-free survival (50% at 5 years).51

A direct comparison of single versus tandem transplantation has been evaluated: in one French study, the projected 7-year event-free and overall survival benefits were significantly better for the tandem arm (10% versus 20% for event-free survival and 21% versus 42% for overall survival, respectively). Other randomized trials have also compared single with double intensive therapy, with only an Italian study showing similar improvement in event-free survival in the tandem group.58–61 Subset analysis of these studies indicated that the second transplant mainly benefits patients who do not enter a very good partial remission (VGPR) (>90% decrease in M protein) or CR following the first transplant. Based on these trials, it is considered the standard of care to perform a second transplant in patients who do not achieve at least a very good remission after the first transplant.

Maintenance Therapy Following Transplant

Two randomized studies have demonstrated the benefit of thalidomide, either as a single agent or in combination, as maintenance therapy after autologous transplantation. In a French trial, thalidomide maintenance improved the 3-year event-free survival compared with observation (52% versus 36%) and 4-year overall survival (87% versus 77%).62 An Arkansas trial showed superior CR rates (62% versus 43%) and 5-year event-free survival with thalidomide (56% versus 44%), but no improvement in overall survival.63 Current trials are evaluating the use of thalidomide plus corticosteroids64,65 or single agent lenalidomide as maintenance.66

Allogeneic Transplant

Even with intense upfront therapy including high-dose therapy with ASCT, almost all patients eventually relapse, and no cures are achieved. Even though data demonstrates long-term survival exceeding 10 years in a minority of patients, there is not a plateau in survival curves as far out as 15 years post-transplant.57 The etiology of the
Relapse is either persistent disease and/or the infusion of contaminating myeloma cells in the stem cell product. Allogeneic transplant offers the advantage of a tumor-free graft source and the proven graft versus myeloma effect by alloreactive donor lymphocytes. Patients surviving allogeneic transplants may have durable molecular CR and a significantly reduced risk of relapse compared with autologous transplants. Conventional myeloablative allogeneic transplants have largely been discarded since they have a prohibitively high TRM that approaches 50% in some studies.

Nonmyeloablative stem cell transplantation or reduced-intensity conditioning (NST/RIC) offer a lower risk of TRM (to the order of 15% at 1 year) while still maintaining a graft versus myeloma effect mediated by donor alloreactivity. The best results have been observed when NST/RIC is performed in newly diagnosed patients with minimal disease following a single autologous transplant. Planned sequential ASCT followed by allogeneic transplants with NST/RIC conditioning remains a promising approach. A recently completed randomized clinical trial comparing tandem autologous transplant versus autologous/NST allogeneic transplant demonstrated a superior long-term outcome in the autologous/NST group. In addition, a similarly designed Blood and Marrow Transplant Clinical Trial Network 0102 trial (over 700 patients) completed accrual in March 2007. To add to the confusion regarding allogeneic transplantation, a European Group for Blood and Marrow Transplantation retrospective analysis comparing conventional allogeneic transplant with NST/RIC

![Signaling Cascades Triggered by Interaction of Multiple Myeloma (MM) Cells and Bone Marrow Stromal Cells (BMSCs). Binding of MM cells to BMSCs triggers both adhesion- and cytokine-mediated MM cell growth, survival, drug resistance, and migration. Multiple myeloma cell binding to BMSCs upregulates cytokine (IL-6, IGF-1, VEGF, and SDF-1α) secretion from both BMSCs and MM cells. These cytokines subsequently activate 3 major signaling pathways (ERK, JAK/STAT3, and/or PI3-K/Akt) and their downstream targets, including cytokines (IL-6, IGF-1, and VEGF) and anti-apoptotic proteins (Bcl-xL, IAPs, and Mcl-1), in MM cells. Adhesion-mediated activation of nuclear factor κB (NF-κB) upregulates adhesion molecules (ICAM-1 and VCAM-1) on both MM cells and BMSCs, further enhancing adhesion of MM cells to BMSCs and cytokine secretion. IL indicates interleukin; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor; SDF, stromal cell-derived factor; ERK, extracellular receptor kinase; JAK, janus kinase; STAT, signal transducer and activators of transcription; IAP, inhibitor of apoptosis; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; TNFα, tumor necrosis factor-α; TGFβ, transforming growth factor-β. Adapted from Hideshima T, Chauhan D, Richardson P, Anderson KC with permission from the Journal of Clinical Oncology.](image-url)
showed an increase in nonrelapse mortality, but a decrease in relapse rates with conventional allogeneic transplant.73 Ideally, a trial should be designed to compare autologous/NST with conventional allogeneic transplant. We conclude that any allogeneic transplant for MM is considered to be investigational and should only be considered in the context of clinical trials.

**EMERGING AGENTS IN CLINICAL TRIALS**

With increased understanding of the interactions between the malignant plasma cell and the bone marrow environment, cell receptor interactions, and intracellular signaling pathways, the number of potential therapeutic targets and novel treatments has grown geometrically. Figure 374 shows some of the important pathways that are currently under investigation. Representative agents currently in clinical trials are shown in Table 7.74 Below are examples of selective agents that target either the myeloma cell, the bone marrow microenvironment, and/or cell surface receptors.

**Targeting Myeloma Cells**

**Akt Inhibition and Recruitment of Death Receptors**

Perifosine (octadecyl-[1,1-dimethyl-piperidinio-4-yl]-phosphate) (Zentaris) is a synthetic novel alkylphospholipid. This is a member of a novel class of antitumor agents that interact with the

| TABLE 7 Novel Agents in Clinical Trials in Multiple Myeloma |
|------------------------------------------------------------|
| **Agents** | **Targets MM Cells** | **Targets Micro-environment** | **Targets Cell Surface Receptors** |
| Thalidomide | + | + |
| Lenalidomide | + | + |
| Bortezomib (Velcade) | + | + |
| Ix/B kinase inhibitor | + | + |
| 2-Methoxyestradiol | + | + |
| Lysophosphatidic acid cyclase inhibitor | + | + |
| Triterpenoid 2-cyano-3, 12-dioxoolean-1, 9-dien-28-oic acid | + | + |
| Alpinimod (Azaspirane) | + | + |
| Shingosine monophosphate 1 inhibitor | + | + |
| R-etabololac | + | + |
| VEGF receptor tyrosine kinase inhibitor (TTK787/ZK222584, GW654652) | + |
| FGFR3 inhibitor (CHIR258) | + |
| Farnesyltransferase inhibitor | + |
| Histone deacetylase inhibitor (LAQ824) | + |
| Heat shock protein-90 inhibitor (17-AAG) | + |
| Telomerase inhibitor (GRN163) | + |
| Inosine monophosphate dehydrogenase (VX-944) | + |
| Rapamycin | + |
| Smac mimetics | + |
| TNF-related apoptosis-inducing ligand (TRAIL)/Apo2 ligand | + |
| IGF-1 receptor inhibitor (ADW) | + |
| HMG-CoA reductase inhibitors | + |
| Anti-Interleukin-6 | + |
| Anti-CD40 (SGN40, CHIR12–12) | + |
| Anti-CD56DM-1 | + |
| Anti-CD138 | + |
| Anti-CS1 | + |
| Anti-CD70 | + |
| Anti-CD74 | + |

MM = multiple myeloma.
TGFβ = transforming growth factor-β.
VEGF = vascular endothelial growth factor.
TNF = tumor necrosis factor.
IGF-1 = insulin-like growth factor-1.
 Modified from Hideshima T, Chauhan D, Richardson P, Anderson KC74 with permission from the Journal of Clinical Oncology.
cell membrane and modulate intracellular growth signal transduction pathways. Perifosine induces significant cytotoxicity in MM cells triggered by c-Jun NH2-terminal kinase activation followed by caspase-8, caspase-9, and poly(ADP-ribose) polymerase cleavage, even in the presence of cytokines (ie, Interleukin-6 [IL-6] and insulin-like growth factor [IGF]-1) or bone marrow stromal cells (BMSCs). Specifically, it inhibits Akt/protein kinase B activity. Akt signaling is important for MM cell survival and antiapoptosis. A Phase II trial of 25 patients treated with perifosine alone resulted in 24% stable disease. When combined with dexamethasone for progressive disease, 3 of 9 patients with evaluable disease had a minimal response, and an additional 2 patients had stable disease for an overall response rate of 55% in heavily pretreated MM patients. Perifosine is also being studied in combination with bortezomib due to the synergistic effects observed in vitro.

**Heat Shock Protein Inhibitors:**
- **Geldanamycin and Tanespimycin**

The heat shock proteins (HSP) are part of a ubiquitous chaperone complex that facilitates the proper folding, prevents misfolding or aggregation, and preserves the 3-dimensional conformation of a number of intracellular proteins. Preclinical studies of HSP90 inhibitors (eg, 17-allylamino-17-demethoxy-geldanamycin [17-AAG]) demonstrated antitumor effects. This agent suppressed proliferation and survival of MM cells both in vitro and in vivo. Clinical trials with HSP90 inhibitors have resulted in minimal activity as single agents, but more promising results have been observed when combined with the proteasome inhibitor bortezomib. A Phase I/II trial combining tanespimycin plus bortezomib showed encouraging preliminary results; responses were seen in all dose levels in both bortezomib-naïve (5/7 pts; 71%); bortezomib-previous treated (5/13 pts; 38%), and bortezomib-refractory (2/6 pts; 33%) patients. Perifosine is also being studied in combination with bortezomib due to the synergistic effects observed in vitro.

**Targeting Myeloma Cells and the Bone Marrow Microenvironment**

**Proteasome Inhibitors: NPI-0052**

NPI-0052 is a novel proteasome inhibitor. Like bortezomib, NPI-0052 triggers apoptosis in MM cells, but is distinct from bortezomib in its chemical structure, effects on proteasome activities, and mechanisms of action. In vitro, both NPI-0052 and bortezomib-triggered apoptosis is associated with sequential occurrence of proteasome inhibition, but with differential kinetics. The cellular response to NPI-0052 occurs much earlier than that to bortezomib. A recent preclinical study demonstrated that orally administered NPI-0052 is cytotoxic to MM cells, with reduced toxicity against normal cells compared with bortezomib. It is currently being evaluated in a Phase I trial. Ultimately, these 2 proteasome inhibitors may be combined since they have different kinetics and cellular responses.

**Targeting Cell Surface Receptors and/or the Bone Marrow Microenvironment**

**Monoclonal Antibodies**

A number of monoclonal antibodies (Mabs) are in clinical trials that target the myeloma cell directly and/or the bone marrow microenvironment. These include Mabs to IGF receptor, IL-6, CD56, CD40, CD138, anti-CS1, CD70, and CD74.

**Anti-IL-6; Tocilizumab**

IL-6 is involved in multiple pathways in myeloma; secretion occurs from the malignant plasma cell, as well as from the microenvironment, resulting in autocrine and paracrine stimulation. This results in myeloma cell proliferation. Tocilizumab, a humanized anti-IL-6 receptor Mab that specifically blocks IL-6 cell-to-cell signaling, is currently being studied in MM. A recent study by Yoshio-Hoshino et al demonstrated in a murine MM model the effectiveness of tocilizumab in vitro and in vivo.

**SUPPORTIVE CARE**

Over the past decade, there have also been significant improvements in supportive care. At some point during their disease course, most patients suffer from the effects of skeletal involvement and anemia.

**Skeletal Lesions**

Skeletal involvement often leads to pain, pathological fractures, and hypercalcemia. These
Complications result from increased osteoclastic bone resorption. Surgical stabilization of the long bones or spine may be necessary in some patients. Local radiation to painful bony disease should be limited to those select patients for whom chemotherapy and/or analgesics have proven unsuccessful.

The mainstay of treatment for skeletal lesions are bisphosphonates (BPs), which are inhibitors of osteoclastic activity. They have been shown to reduce skeletal complications and skeletal morbidity and to improve quality of life. In the United States, the preferred BPs in oncology are the intravenous formulations of pamidronate or zoledronic acid due to the markedly greater activity and bioavailability compared with oral BPs. In Europe, clodronate, an oral BP, has shown efficacy.

Bisphosphonates are administered monthly. The major side effects associated with prolonged BP use include nephritic syndrome, renal insufficiency, hypocalcemia, and osteonecrosis of the jaw (ONJ). The incidence of ONJ has recently been shown to be associated with prolonged use of BPs (>1 year) and is more frequently reported with zoledronic acid than pamidronate. Studies are currently underway to address whether the benefits of BPs can be realized if they are given on a less frequent schedule in an attempt to decrease the incidence of complications.

The Mayo Clinic myeloma group has recently published their consensus guidelines for BP use (Table 8). These guidelines are similar to the updated BP guidelines from the American Society of Clinical Oncology. In response to the Mayo Clinic consensus guidelines, the International Myeloma Working Group, which comprises over 70 investigators specialized in the area of MM, has reviewed and considered the “Mayo Clinical Consensus Statement.” Although there is general agreement with the Mayo Clinic

| Clinical Scenario                                      | Guideline                                                                 |
|-------------------------------------------------------|----------------------------------------------------------------------------|
| MM and lytic disease evident on plain radiographs     | IV bisphosphonates should be administered monthly for patients with MM and lytic disease evident on plain radiographs |
| Osteopenia or osteoporosis, but no lytic disease       | It is reasonable to start IV bisphosphonates in these patients with MM who do not have lytic bone disease if osteopenia or osteoporosis is evident on bone mineral density studies, but not in patients with normal results on bone density studies |
| mineral density studies                               |                                                                            |
| Smoldering MM                                          | Bisphosphonates are not recommended for patients with smoldering MM; bisphosphonate therapy should be used only in the setting of a clinical trial |
| Duration of bisphosphonate therapy                    | Patients should receive infusion of bisphosphonates monthly for 2 years; after 2 years, if the patient has achieved remission and is in stable plateau phase off treatment, the bisphosphonate can be discontinued, but if the MM still requires active treatment, the frequency of bisphosphonate infusions can be decreased to every 3 months |
| Choice of bisphosphonate                              |                                                                            |
| Dental evaluation and follow up of patients taking    | Encourage patients to do the following:                                   |
| bisphosphonates                                       | Have comprehensive dental evaluations before receiving any bisphosphonate treatment |
|                                                      | Undergo invasive dental procedures before starting bisphosphonate treatment |
|                                                      | See a dentist at least annually and maximize preventive care; report oral/dental symptoms promptly |
|                                                      | Manage new dental problems conservatively and avoid dental extractions unless absolutely necessary |
|                                                      | See an oral and maxillofacial surgeon if surgery is required |
|                                                      | Practice good dental hygiene |
|                                                      | Encourage physicians to withhold bisphosphonate treatment for at least 1 month before the procedure, and do not resume until the patient has fully recovered and healing of the surgery is complete |

MM = multiple myeloma.
Modified from Lacy MQ, Dispenzieri A, Gertz MA, et al with permission from Mayo Clinic Proceedings.
myeloma group’s statement, the International Myeloma Working Group also recommends the following:

- BP therapy is not indicated in patients with smoldering/inactive myeloma outside of a clinical trial.
- If radiographs are negative or show only osteopenia or osteoporosis, there is no simple agreed-upon strategy.
- Bone density measurement is not widely used, but can help document and quantitate diffuse osteopenia/osteoporosis. However, this does not indicate any causal relationship with regard to myeloma.
- BP use should no longer be indefinite or open-ended. The duration of BP therapy should be modified based on the evidence of ongoing active bone disease. As a routine recommendation, 2 years of therapy is considered very reasonable.
- In the post-transplant setting and/or in the nontransplant setting in patients who have achieved CR or VGPR with novel and/or other therapies, 1 year is considered reasonable if there is no evidence of active bone disease. Conversely, longer therapy is justified if there is evidence of continued active bone disease in patients with lesser degrees of response.
- As noted by the Mayo Clinic, ONJ is the major new concern with chronic BP use. Use of pamidronate or clodronate confers the lowest risk, especially with 1 to 2 year’s duration of therapy plus dental precautions. The risk of ONJ with pamidronate is ≤1% to 2% within the first 2 years and 0% to 0.5% with clodronate (only rare cases reported). The risk with zoledronic acid is approximately 2-fold higher versus pamidronate.
- There is near unanimity that pamidronate is the safest intravenous BP with at least equivalency with regard to efficacy (with respect to reduction in skeletal related events) compared with other BPs.

For patients with vertebral body compression fractures, there are 2 technologies that can alleviate pain: vertebroplasty (injection of methylmethacrylate into a collapsed vertebral body) and kyphoplasty (introduction of an inflatable balloon into the vertebral body and after inflation, injection of methylmethacrylate into the cavity). Both technologies have proven effective in up to 85% of patients, particularly those with compression fractures of less than 1 year in duration. Pain relief is virtually immediate. Risks of the procedure are minimal and include rare infections, bleeding, or leakage of the methylmethacrylate from the site.

Spinal cord compression from an extramedullary plasmacytoma is a true emergency. This should be considered in the differential diagnosis in patients with back pain and/or neurologic symptoms (eg, lower extremity weakness, bowel or bladder dysfunction, paresthesias). If a spinal cord compression is suspected, an MRI of the entire spine should be performed immediately. Standard treatment for cord compressions (high-dose corticosteroids and radiation therapy) should be followed. Rarely, surgical intervention is required.

Renal Insufficiency

Renal insufficiency occurs in approximately 15% of patients at diagnosis and up to 25% over the course of their disease. The etiology of renal insufficiency includes light chain cast nephropathy, light chain deposition disease, hypercalcemia, and amyloidosis. Volume depletion, infection, and nonsteroidal anti-inflammatory agents for analgesia may also contribute to renal failure. Nonsteroidal inflammatory agents and contrast media should be avoided when possible and renal function carefully monitored if these agents are required. Patients should be instructed to drink a minimum of 2 L/day to maintain a high urine output. There are proponents of plasmapheresis in MM patients who present with acute renal failure. However, a recent randomized trial did not demonstrate a benefit for plasmapheresis. Patients who present with renal insufficiency should be treated aggressively in an attempt to normalize renal function as quickly as possible. Up to 50% of patients with renal insufficiency will improve with initial therapy. The choice of therapy is dependent on the metabolism of the chemotherapeutic agents. For example, bortezomib can be safely administered, even in patients on hemodialysis.

Anemia

Anemia occurs in almost all MM patients during their disease course. The etiology may be
multifactorial: suppression of erythropoiesis by tumor-related cytokines, secondary to chemotherapy, renal insufficiency, and/or vitamin or iron deficiency. Treatment of the underlying disease improves erythropoiesis in many patients. Randomized placebo-controlled trials have shown that symptomatic anemia often is improved by administration of exogenous erythropoietin. Up to 65% of patients respond to erythropoietin injections, even in the absence of renal insufficiency. Improvement in anemia results in significantly enhanced quality of life. Erythropoietin (40,000 U subcutaneously weekly) or darbepoietin (200 mcg subcutaneously every 2 weeks or 500 mcg subcutaneously every 3 weeks) improves hemoglobin concentration and reduces transfusion requirements. In addition, there is preliminary evidence that the use of erythropoietin may improve survival in patients with advanced myeloma, possibly by enhancement of antmyeloma immune mechanisms. Once the target hemoglobin has been achieved (>12 g/dL), the erythropoietic agent should be discontinued or changed to a maintenance dose. Based on the recent evidence that hemoglobin levels exceeding 13 g/dL were associated with an increased risk of death in nonmyeloma dialysis-dependent patients on erythropoietin, continuation beyond the 12 g/dL range should be avoided. Particular care should be followed in patients on erythropoietic agents in combination with immunomodulatory drugs and high-dose corticosteroids—the risk of venous thromboembolic events is 15% to 20%. These patients should receive thromboprophylaxis with either aspirin, warfarin, or low-molecular weight heparin. The choice of thromboprophylactic agent should be risk-based: full-dose anticoagulation for a patient on all 3 agents and lesser levels of thromboprophylaxis for patients at lower risk (eg, low-dose corticosteroids).

Infections

Infections are common in MM patients in part due to decreased production of normal immunoglobulins. Patients who present with fever should be evaluated with appropriate cultures and radiographic studies and started on antibiotics. Infections by encapsulated organisms (eg, Streptococcal infections) are a particular concern and should be appropriately covered. Fever is rarely due to myeloma itself, and an infectious etiology should be sought. The use of prophylactic antibiotics in MM has not been resolved. A small randomized placebo-controlled clinical trial comparing trimethoprim-sulfmethoxazole (TMP-SMX) in 57 newly diagnosed MM patients showed benefit with routine prophylaxis the first 2 cycles of therapy. To further investigate the importance of prophylactic antibiotics, there is a large randomized ECOG Phase III trial comparing fluoroquinolones versus TMP-SMX versus observation in newly diagnosed patients during the first 2 months of therapy. Many clinicians utilize prophylactic antibiotics, such as double-strength TMP-SMX or fluoroquinolones (ie, ciprofloxan, moxifloxin) either on a daily basis or on a Monday-Wednesday-Friday basis. Although an important pathogen when it occurs, Pneumocystis carinii pneumonia is infrequently observed in MM, even with the use of high-dose corticosteroids. For patients with recurrent documented bacterial infections in the setting of hypogammaglobulinemia, one should consider prophylactic intravenous immunoglobulins 500 mg/kg monthly.

Even in patients on high-dose corticosteroids, antifungal antibiotics are usually not required outside of the peritransplant setting. In addition to defects in humoral immunity, MM patients also have defects in their cell-mediated immunity. Without prophylaxis, up to 20% of MM patients may develop varicella-zoster virus infections. This is particularly true in patients receiving bortezomib chemotherapy, for which rates as high as 30% have been reported. The use of antiviral antibiotics such as acyclovir or its analogs should be considered in MM patients. It should certainly be prescribed for patients receiving bortezomib. The most common regimen for acyclovir is 400 mg twice daily Monday-Wednesday-Friday.

Finally, the efficacy of vaccinations in MM patients is highly variable and remains an area of clinical uncertainty. There is no medical contraindication to vaccinations in these patients, so many patients in clinical practice are given annual influenza vaccinations and a single pneumococcal vaccination. The newly available varicella-zoster virus vaccine is a live virus and
is not currently recommended for patients with lymphoproliferative diseases.

**FUTURE DIRECTIONS**

There is reason for optimism in the treatment of MM. The use of conventional agents, novel agents, combination therapies, and HSCT is responsible for markedly improved outcomes. For example, the overall median survival for patients enrolled in clinical trials has improved from 3 years in the decades from 1960 to 1990 to 5 years from 1990 to 2000. We project that optimizing current regimens and employing investigational agents will result in median survivals exceeding 7 years within the next 10 years.

It appears likely that there will be future modifications of the ISS incorporating FISH and GEP. These technologies will further define patients at highest risk for rapid progression of their disease. Not only will this help to identify patients who may benefit from the most aggressive interventions, but it may eventually lead to regimens that are specifically tailored to the genetic profile of their particular myeloma. With this in mind, clinicians can optimistically anticipate a future when MM will no longer be thought of as a terminal illness but, instead, a chronic disease with multiple treatment options associated with prolonged survival and a good quality of life.

**PATIENT RESOURCES**

The MM patient community is quite close-knit through support groups and Internet chat rooms. There are a number of excellent resources for patient support, including the ACS (www.cancer.org), Leukemia & Lymphoma Society (www.lls.org), International Myeloma Foundation (www.myeloma.org), and the Multiple Myeloma Research Foundation (www.multiplemyeloma.org).

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