Management of Relapsed and Relapsed/Refractory Multiple Myeloma

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Key Words

Multiple myeloma, lenalidomide, bortezomib, stem cell transplantation

Abstract

Despite significant progress in the treatment of multiple myeloma (MM) over the past decade, this disease remains incurable and almost all patients ultimately experience relapse and become refractory to treatment over time. However, the outlook for patients with relapsed MM has improved markedly with the use of the immunomodulatory drugs thalidomide and lenalidomide, and the proteasome inhibitor bortezomib. Moreover, the development of new drug classes based on preclinical rationale and the introduction of next-generation agents is likely to further expand treatment options and improve outcomes for relapsed MM. (*JNCCN* 2011;9:1209–1216)

Multiple myeloma (MM) is a B-cell neoplasm characterized by aberrant expansion of plasma cells within the bone marrow and extramedullary sites, including cortical bone. It accounts for 10% to 15% of hematologic malignancies, and 20% of deaths related to cancers of the blood and bone marrow.¹ In most cases, MM evolves from a preexisting monoclonal gammopathy of undetermined significance.² The neoplastic clone derives from a post-germinal center

B cell, as suggested by the presence of clonally rearranged immunoglobulin light (IgL) and heavy (IgH) chains. Chromosomal abnormalities are detected with conventional cytogenetics or fluorescence in situ hybridization (FISH) in more than 90% of patients, and include deletions, trisomies, and translocations.³ Hyperdiploidy and IgH translocations seem to be early genetic events in the pathogenesis of MM, whereas del(17p13) and translocations involving the MYC locus represent later events.⁴ Interactions between malignant plasma cells and the stromal microenvironment play an important role in tumor growth.⁵ Prognosis in MM is assessed based on chromosomal abnormalities,⁶ the International Staging System (ISS),⁷ and clinical characteristics such as the presence of renal impairment or extramedullary disease.

Induction regimens that incorporate thalidomide, lenalidomide, and/or bortezomib are now standard for newly diagnosed MM in the United States.^{8–12} Eligible patients may undergo autologous stem cell transplantation (ASCT), which deepens and prolongs the therapeutic response.¹³ Post-ASCT maintenance therapy with thalidomide has been associated with improvement in progression-free and overall survivals,^{14,15} but long-term use is limited by therapy-associated toxicity, particularly peripheral neuropathy. Maintenance therapy with lenalidomide is currently being evaluated in 2 phase III clinical trials.^{16,17} To date, both studies have shown a progression-free survival benefit associated with lenalidomide maintenance therapy, whereas in the most recent interim analysis, one of the studies shows an overall survival advantage.

The current approach to management of newly diagnosed MM has markedly improved outcomes.^{18,19} However, even patients who have an excellent response with initial therapy ultimately experience relapse and require further therapy. Prognosis associated with re-

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Submitted June 8, 2011; accepted for publication September 2, 2011.

Dr. Richardson serves on the advisory board for Millennium Pharmaceuticals, Inc., Celgene Corporation, Novartis, Johnson & Johnson, and Bristol-Myers Squibb. All other authors have disclosed that they have no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in this article or their competitors.

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lapsed MM is generally poor, with a median overall survival of less than 1 year among patients who have received 2 or more prior lines of therapy.²⁰

Definition of Relapsed and Relapsed/Refractory MM

The European Group for Blood and Marrow Transplantation²¹ criteria and International Myeloma Working Group uniform criteria²² provide standard definitions for relapsed MM. Relapsed MM is defined as disease that progresses and requires salvage therapy. Relapsed and refractory MM is defined as disease that is nonresponsive to salvage therapy or progresses within 60 days of the last treatment in patients who previously experienced at least a minimal response. These entities are distinguished from primary refractory MM, which refers to disease that fails to achieve at least a minimal response with initial therapy.

Diagnostic Evaluation

The evaluation of a patient with relapsed MM focuses on identifying sites of disease involvement and establishing prognosis. Laboratory studies include a comprehensive metabolic panel, CBC with differential, serum protein electrophoresis with immunofixation, 24-hour urine for both total protein and urine protein electrophoresis with immunofixation, quantitative immunoglobulins, serum-free light chain analysis, and lactate dehydrogenase (LDH). The prognostic value of β_2 -microglobulin at the time of relapse is uncertain. Serum viscosity should be measured when hyperviscosity is suspected.

Bone marrow evaluation is not always necessary but should be performed in cases of nonsecretory or oligosecretory disease and when a secondary bone marrow process, such as myelodysplasia, is suspected. When bone marrow evaluation is performed, metaphase cytogenetics and FISH analysis are recommended, because new chromosomal abnormalities may be identified.

A skeletal bone survey is often obtained to identify new areas of skeletal disease. An MRI should be performed to evaluate musculoskeletal pain and neurologic symptoms that suggest cranial nerve, spinal cord, or peripheral nerve involvement. The role

of FDG-PET is being evaluated in MM. In patients with relapsed disease, this modality may be useful in the presence of an elevated LDH or when extramedullary involvement is suspected.

Determinants of Therapy

Disease characteristics, characteristics of prior or ongoing therapy, and patient characteristics are important determinants of therapy for relapsed MM (Table 1).

Disease Characteristics

Chromosomal abnormalities associated with high-risk MM, such as del(17p), may be detected in patients who previously had standard-risk MM based on chromosomal analysis at diagnosis. As in newly diagnosed disease, adverse cytogenetic abnormalities detected at relapse portend a poor outcome.²³ Patients with high-risk cytogenetics at diagnosis retain that designation throughout the disease course.

Clinical manifestations often evolve during the disease course. Patients with previously indolent disease may experience relapse with an aggressive clinical phenotype characterized by extensive organ dysfunction or extramedullary disease. A comprehensive history, physical examination, and laboratory evaluation at relapse are therefore essential to guide management.

Characteristics of Prior or Ongoing Therapy

Assessment of patients with relapsed MM includes a thorough review of previous and ongoing therapies, duration of prior therapies, and both depth and dura-

Table 1 Determinants of Therapy in Relapsed Multiple Myeloma

<i>Disease Characteristics</i>
<ul style="list-style-type: none">• High- versus standard-risk cytogenetics• Abnormal versus intact organ function• Presence versus absence of extramedullary disease
<i>Characteristics of Prior or Ongoing Therapy</i>
<ul style="list-style-type: none">• Short versus prolonged response to prior therapy• Progression on current therapy• Toxicities associated with prior therapy
<i>Patient Characteristics</i>
<ul style="list-style-type: none">• Performance status• Comorbid medical conditions• Preference regarding mode of chemotherapy administration• Overall goals of care

tion of response to prior treatment. Short duration of response and progression while on therapy are associated with adverse outcome.^{24,25} Previous treatment-related toxicities are reviewed and attributed to a specific agent when possible.

Patient Characteristics

Disease-independent patient characteristics such as performance status, comorbid conditions, and goals of care influence treatment decisions. Patients with limited performance status may require dose or schedule adjustments to minimize treatment-related toxicities. Comorbid conditions, such as congestive heart disease, cerebrovascular disease, and poorly controlled diabetes mellitus, require optimization to allow the patient to tolerate therapy. Finally, patient preferences regarding mode of chemotherapy administration, duration of therapy, and goals of care will impact choice of therapy and must be elicited before initiation of therapy.

General Approach to Management of Relapsed MM

Treatment Algorithm

Patients are risk stratified according to the current cytogenetic and clinical features of the disease, and previous response to therapies. Patients with adverse cytogenetics, aggressive clinical features, short duration of response to prior therapy, or progression on current treatment are classified as having high-risk disease. Those with absence of adverse cytogenetics, indolent clinical features, and prolonged response to previous therapy are classified as having standard-risk relapsed MM.

Patients who are naïve to an agent with known activity in MM are typically treated with a regimen incorporating this agent. In this context, assessment to determine ASCT eligibility is important; patients with relapsed MM who have not previously undergone ASCT can be considered for high-dose therapy, as can patients who experienced a prolonged response to first ASCT. Patients whose disease previously responded to a particular agent can be re-treated at relapse with the same drug alone or in combination with other agents.^{26,27} Moreover, patients whose disease previously showed resistance to a specific drug may be treated with that drug in combination with other agents with which synergy exists.

Finally, patient characteristics such as performance status, comorbidities, and preferences regarding goals of care are reviewed, because these factors influence treatment choice, dose, and schedule.

Approach to High-Risk Disease

Patients with high-risk disease are generally treated with highly active 3- or 4-drug combinations for maximal response. Appropriately selected patients whose disease responds to initial therapy in the relapsed setting can then be considered for ASCT.

Allogeneic SCT represents an option for a subset of patients whose disease responds to treatment and who have an available human leukocyte antigen-matched donor, chemotherapy-sensitive disease, and excellent performance status.

A potential graft-versus-myeloma effect has stimulated interest in allogeneic stem cell transplant for high-risk patients,²⁸ but application of this modality has been limited because of high rates of treatment-related mortality (TRM). Advances in supportive care and use of reduced-intensity, nonmyeloablative conditioning regimens have contributed to a lower rate of TRM,²⁹ but transplant-related toxicity remains a significant concern; therefore, it is generally recommended that allogeneic transplant be performed in the context of a clinical trial whenever possible.³⁰ Likewise, high-risk patients who are chemotherapy-resistant should be referred for participation in clinical trial.

Approach to Standard-Risk Disease

Patients with standard-risk relapsed MM are generally treated with 1- or 2-drug regimens that include an agent to which the patient is either naïve or has known sensitivity. As in the case of high-risk disease, consolidative high-dose therapy with ASCT can be considered for patients without prior exposure to high-dose therapy and those who sustained a prolonged response to prior transplant. Clinical trial participation is an important option for standard-risk relapsed MM.

Duration of Therapy

Duration of therapy in relapsed MM is determined by the clinical context. Patients with aggressive, high-risk relapsed disease are likely to progress without ongoing therapy and typically require continuous therapy, although short treatment-free intervals may be necessary during transition from one regimen to another or for necessary surgical/radiation interventions. In patients with standard-risk relapsed

disease who respond to treatment, options include consolidation with ASCT, maintenance therapy with an agent to which the disease is sensitive, or observation without therapy.

Treatment Options in Relapsed MM

Thalidomide-Based Regimens

The efficacy of single-agent thalidomide was established in a phase II trial in which 84 individuals with relapsed and refractory MM received thalidomide at daily doses ranging from 200 to 800 mg.³¹ The overall response rate was 32%, with 2-year event-free and overall survival rates of 20% and 48%, respectively.³² These results were confirmed by other studies of single-agent thalidomide in relapsed MM in which response rates ranged from 14% to 48%.^{33–40}

Although thalidomide can be used as a single agent, it is more often given in conjunction with dexamethasone.^{41–44} In a phase II study,⁴² 44 patients with refractory MM received thalidomide 200 mg/d, with dose escalation to 400 mg/d along with pulsed doses of dexamethasone. Despite the fact that 77% of patients were resistant to prior dexamethasone-containing therapy, thalidomide-dexamethasone led to a partial response rate of 55%, with comparable activity among patients resistant to previous dexamethasone-containing regimens and those who were not.

Thalidomide can also be used with conventional chemotherapeutic agents. The combination of dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DTPACE) is an example of this approach. DTPACE was evaluated in a study involving 236 individuals with relapsed and refractory MM, 63% of whom had experienced progression on their previous line of therapy and 23% of whom had chromosome 13 abnormalities.⁴⁵ The regimen produced a partial response rate of 32% and a complete response (CR)/near CR (nCR) rate of 16%.

Sedation, fatigue, and constipation are common toxicities with thalidomide. Peripheral neuropathy caused by axonal injury and loss of large-diameter myelinated nerve fibers is dose- and time-dependent.^{46,47} Venous thromboembolism occurred in 2% to 15% of patients with relapsed MM receiving thalidomide and either dexamethasone or chemotherapy.⁴⁸ Other less common but important toxicities include bradycardia,⁴⁹ hypothyroidism,⁵⁰ and rash.⁵¹

Lenalidomide-Based Regimens

The efficacy of lenalidomide in combination with dexamethasone (LD) in relapsed MM was established by 2 phase III studies comparing LD to dexamethasone alone in patients with relapsed or relapsed/refractory MM (MM-009 and MM-010).^{52,53} Patients who received LD had a superior overall response rate compared with placebo-dexamethasone (MM-009: 61% vs. 19.9%; $P < .001$; MM-010: 60.2% vs. 24%; $P < .001$) in both studies. The superior response to LD translated into clinical benefit, with prolonged median time to progression (MM-009: 11.1 vs. 4.7 months; $P < .001$; MM-010: 11.3 vs. 4.7 months; $P < .001$) and median overall survival (MM-009: median overall survival, 29.6 vs. 20.2 months; $P < .001$; MM-010: hazard ratio for death, 0.66; $P = .03$). The benefit of LD was observed regardless of prior thalidomide exposure.⁵⁴ Patients who received LD in first relapse fared better than those who had received 2 or more prior therapies in terms of time to progression, progression-free survival, and overall survival.⁵⁵

The lenalidomide, cyclophosphamide, and dexamethasone regimen can also be used in the relapsed setting.⁵⁶ This combination was evaluated in a phase I/II study in which the overall response rate was 65%, the CR rate was 5%, and the rate of very good partial response or better was 15%.

Myelosuppression is the most common high-grade toxicity associated with lenalidomide. Lenalidomide is also associated with an increased risk of venous thromboembolism, and therefore thromboprophylaxis is necessary.^{52,53} A macular rash occurs in up to 30% of patients who receive lenalidomide,⁵⁷ but it is usually mild and resolves with either topical corticosteroid therapy or brief interruption of therapy. Dose adjustment is necessary in patients with impaired renal function to avoid drug-related side effects.⁵⁸

Bortezomib-Based Regimens

The efficacy of bortezomib in relapsed and relapsed/refractory MM was shown conclusively in a randomized phase III study comparing bortezomib and high-dose dexamethasone.⁵⁹ Bortezomib was superior to high-dose dexamethasone with respect to all clinical end points, including overall response rate (38% vs. 18%; $P < .001$), median time to progression (6.2 vs. 3.5 months; $P = .001$), and 1-year overall survival (80% vs. 66%; $P = .003$). A survival benefit was seen despite a 62% crossover rate from the dexa-

methasone to the bortezomib treatment arm. The clinical benefit of bortezomib relative to high-dose dexamethasone was independent of type and extent of prior therapy.⁶⁰ Depth of response correlated with clinical benefit, with patients experiencing a CR having longer median treatment-free intervals and time to alternate therapy.⁶¹

The combination of bortezomib and pegylated liposomal doxorubicin was shown to be effective in relapsed MM in a phase III study comparing this combination with bortezomib alone.⁶² The doublet yielded superior time to progression (9.3 vs. 6.5 months; $P = .000004$) and 15-month overall survival (76% vs. 65%; $P = .03$). The response rate and median time to progression were comparable in patients with and without renal insufficiency (creatinine clearance < 60 mL/min), although the incidence of drug-related toxicities was higher among those with impaired renal function.⁶³

The combination of bortezomib, oral cyclophosphamide, and prednisone is well tolerated and active in relapsed MM. In a phase I/II, this regimen yielded an overall response rate (minimal response or better) of 95% and a CR rate of approximately 50%.⁶⁴ The 1-year progression-free and overall survival rates at the highest dose level were 83% and 100%, respectively.

Toxicities with bortezomib include peripheral neuropathy, thrombocytopenia, and diarrhea. Bortezomib-associated peripheral neuropathy is cumulative and dose-related, and symptom-guided dose modification based on a standard dose reduction algorithm is recommended.⁶⁵ Thrombocytopenia is usually cyclic, with a decline followed by recovery during the period off therapy.⁶⁶ Bortezomib is associated with an increased incidence of herpes zoster reactivation, and therefore antiviral prophylaxis is recommended.⁵⁹ Rare instances of lung injury have been reported, including bronchiolitis obliterans with organizing pneumonia⁶⁷ and pulmonary fibrosis.⁶⁸

Combinations of an Immunomodulatory Drug and Bortezomib

High levels of response have been achieved with combinations that incorporate both bortezomib and either thalidomide or lenalidomide. This is consistent with preclinical data showing synergy between these drug classes.⁶⁹ In a phase I/II study, 85 patients received bortezomib in combination with thalidomide, with dexamethasone added for suboptimal re-

sponse after 3 cycles.⁷⁰ The bortezomib, thalidomide, and dexamethasone combination yielded an overall response rate (minimal response or better) of 79%, a partial response rate of 63%, and an nCR rate of 22%. The 4-year event-free and overall survival rates were 6% and 23%, respectively.

In the authors' phase I study evaluating lenalidomide and bortezomib in relapsed MM, the most common grade 3/4 therapy-related toxicities were neutropenia, thrombocytopenia, anemia, and leukopenia.⁷¹ Sensory peripheral neuropathy occurred in 42% of patients, although no episodes of grade 3/4 peripheral neuropathy were seen. The overall response rate (minimal response or better) was 61%, with a CR/nCR rate of 8%; median overall survival was 37 months. In a subsequent phase II study, lenalidomide, bortezomib, and dexamethasone produced an overall response rate (minimal response or better) of 86% and a CR/nCR rate of 24%.

New Agents in Relapsed MM

Numerous novel compounds are being evaluated in relapsed MM (Table 2). Promising results have been observed, for example, with the new immunomodulatory agent pomalidomide (CC4047) and the proteasome inhibitor carfilzomib. In phase II studies, pomalidomide showed significant anti-MM activity even in patients with high-risk disease and those who have thalidomide-, lenalidomide-, or bortezomib-refractory disease.^{72,73} Carfilzomib, which irreversibly inhibits the 20S proteasome, was also proven to be active in relapsed MM and is associated with minimal treatment-related peripheral neuropathy.^{74,75}

Perifosine, a small molecule inhibitor of the phosphatidylinositol 3-kinase (PI3-K/AKT) pathway, has been evaluated in conjunction with lenalidomide⁷⁶ and in combination with bortezomib.⁷⁷ It is currently being assessed in a phase III study of bortezomib and dexamethasone plus perifosine/placebo.

The histone deacetylase (HDAC) inhibitors vorinostat, panobinostat, and romidepsin are currently being evaluated in relapsed MM. Although these agents have modest single-agent activity, they possess significant anti-MM effect in combination with agents such as lenalidomide⁷⁸ or bortezomib.^{79,80}

Monoclonal antibody therapy targeting plasma cell antigens such as the CS1 glycoprotein and CD38 is a promising approach in relapsed MM. The

Table 2 New Agents in Development for the Treatment of Relapsed Multiple Myeloma

Agent	Mechanism of Action	Stage of Development
Carfilzomib	Proteasome inhibitor	Phase II/III
NPI-0052	Proteasome inhibitor	Phase II
Pomalidomide	Immunomodulator (IMiD, 3rd generation)	Phase III
CNTO 328	Monoclonal antibody against interleukin-6	Phase II
Elotuzumab	Humanized monoclonal antibody directed against CS1	Phase III
Perifosine	Akt inhibitor	Phase II/III
Vorinostat	HDAC inhibitor	Phase III
Panobinostat	HDAC inhibitor	Phase III
Temsirolimus	mTOR inhibitor	Phase I/II
Plitidepsin (aplidin)	Jun N-terminal kinase (JNK) activator, antiangiogenic activity	Phase II/III

Abbreviations: HDAC, histone deacetylase; mTOR, mammalian target of rapamycin.

anti-CS1 monoclonal antibody elotuzumab and the anti-CD38 antibody daratumumab are examples of monoclonal antibodies currently being investigated.

Conclusions

Management of relapsed MM requires a comprehensive approach based on the unique features of each patient. Patients are risk-stratified at relapse based on chromosomal abnormalities and clinical characteristics, such as renal failure and extramedullary involvement. Response to prior therapy is also a critical determinant of treatment. Appropriate therapy is administered based on these considerations, using regimens that typically incorporate thalidomide, lenalidomide, and/or bortezomib. Despite overall improvement in patient outcomes, relapsed/refractory MM remains a challenging clinical situation and an important area of investigation. A variety of novel agents are currently being evaluated in relapsed MM, and based on this research, treatment options and patient outcomes are expected to further improve.

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Relapsed/Refractory Multiple Myeloma

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