Original Article

Novel Therapies in the Treatment of Multiple Myeloma

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Key Words

Multiple myeloma, cytogenetics, chemotherapy, thalidomide, lenalidomide, bortezomib

Abstract

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by aberrant expansion of plasma cells within bone marrow and extramedullary sites. In 2009, 20,580 new cases of MM and 10,580 deaths from the disease occurred in the United States. Treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation or surgery in selected cases associated with extramedullary disease. The therapeutic landscape in MM has changed markedly in the past decade with the introduction of the novel immunomodulatory agents thalidomide and lenalidomide, and the first-in-class proteasome inhibitor bortezomib. Although MM remains an incurable malignancy, new approaches to therapy incorporating these agents have produced significantly higher response rates and improved intervals of both progression-free and overall survival in the context of randomized, controlled trials. In aggregate, the use of novel therapies in MM has been associated with substantial improvements in patient outcome. (*JNCCN* 2009;7:947–960)

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Multiple myeloma (MM) is a clonal B-cell malignancy characterized by aberrant expansion of plasma cells within the bone marrow and extramedullary sites.[1] In 2009, 20,580 new cases and 10,580 deaths from the disease are estimated to occur in the United States.[2] Treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation or surgery in selected cases associated with extramedullary disease. The therapeutic landscape in MM has changed markedly in the past decade with the introduction of the novel immunomodulatory agents (IMiDs) thalidomide and lenalidomide, and the first-in-class proteasome inhibitor bortezomib. Although MM remains an incurable malignancy, new approaches to therapy incorporating these agents have produced significantly higher response rates and improved intervals of both progression-free (PFS) and overall survival (OS) in the context of randomized, controlled trials. In aggregate, the use of novel therapies in MM has been associated with substantial improvements in patient outcome.[3]

The 2009 NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org) reflect the promising results associated with therapies incorporating thalidomide, lenalidomide, and bortezomib.[4] These guidelines include various regimens incorporating novel agents in combination with dexamethasone, conventional chemotherapeutic agents, and other novel agents.

Table 1 Diagnosis of Multiple Myeloma

Smoldering Myeloma	Active Myeloma
Serum monoclonal protein ≥ 3 g/dL and/or: Bone marrow clonal plasma cells > 10% No evidence of organ or tissue impairment or symptoms related to multiple myeloma	Presence of serum or urine monoclonal protein (except in cases of nonsecretory myeloma) and bone marrow clonal plasma cells ≥ 10% with one of the following: • Elevated calcium (> 11.5 g/dL) • Renal insufficiency (creatinine > 2 mg/dL) • Anemia (hemoglobin < 10, or 2 g < normal) • Bone disease (lytic or osteopenic) • Other manifestation of active myeloma, including repeat infections, hyperviscosity, hypogammaglobulinemia, or secondary amyloidosis

Diagnosis, Staging, and Risk Stratification

MM is diagnosed based on the presence of a monoclonal protein or significant (≥ 10%) involvement of the cellular bone marrow, along with evidence of end organ damage as manifested by elevated serum calcium (≥ 11.5 g/dL), renal insufficiency (serum creatinine ≥ 2 mg/dL), anemia (hemoglobin ≤ 10 g/dL or 2 g below normal), or lytic bone lesions[4,5] (Table 1). Symptoms and signs may suggest secondary amyloidosis or hyperviscosity, and should be assessed during the diagnostic workup.

Once MM is diagnosed, patients are classified according to 2 staging systems (Table 2). The first of these, the Durie-Salmon system, provides a measure of tumor burden using the number of myeloma-related bone lesions seen on radiograph and concentrations of serum calcium, serum monoclonal protein, and urine Bence-Jones protein to classify patients as having stage I, II, or III disease.[6] The International Staging System (ISS), however, provides a measure of proliferative tumor and prognostic information.[7] Based on multivariate analysis of clinical features present at treatment initiation, the ISS uses serum β_2-microglobulin (β_2M) and serum albumin to cat-

Table 2 Durie-Salmon Staging System and International Staging System

Stage	Durie-Salmon Staging System	International Staging System
I	Hemoglobin > 10 g/dL	β_2M ≤ 3.5 g/dL and albumin ≥ 3.5 g/dL
	Calcium normal or ≤ 12 mg/dL	
	Normal skeletal survey or solitary plasmacytoma	
	Low M-protein production:	
	• IgG < 5 g/dL	
	• IgA < 3 g/dL	
	Bence Jones protein < 4 g/24 hr	
II	Neither stage I nor III	Neither stage I nor II
III	One of the following:	β_2M ≥ 5.5 g/dL
	• Hemoglobin < 8.5 g/dL	
	• Calcium > 12 mg/dL	
	• Multiple lytic bone lesions	
	• High M-protein component:	
	▸ IgG > 7 g/dL	
	▸ IgA > 5 g/dL	
	• Bence Jones protein > 12 g/24 hr	

Durie-Salmon subclassification of A or B: A, renal function (creatinine < 2.5 mg/dL); B, abnormal renal function (creatinine > 2.0 mg/dL).
Abbreviations: β_2M, β_2-microglobulin; Ig, immunoglobulin; M-protein, monoclonal protein.

egorize patients as having stage I (median survival, 62 months), stage II (median survival, 44 months), or stage III (median survival, 29 months) disease.[7]

In addition to the ISS, genetic analysis of malignant plasma cells provides important insights into prognosis in MM. As part of the initial diagnostic evaluation for MM, NCCN recommends conventional metaphase cytogenetics and fluorescence in situ hybridization (FISH) analysis for del 13, del 17, t(4;14), t(11;14), and t(14;16).[4] Hyperdiploidy has been associated with a favorable prognosis; t(11;14) with an intermediate prognosis; and hypodiploidy, t(4;14), t(14;16), t(14;20), and del 17, with a poor prognosis.[8–11] Del 13 by metaphase karyotype, although not by interphase FISH analysis, is also consistently associated with a poor prognosis in MM.[8,12]

Gene expression profiling (GEP) based on microarray analysis of mRNA derived from CD138-enriched plasma cells was recently used to classify patients with MM.[13,14] In an analysis of various prognostic models used to characterize 220 patients who underwent treatment in the Total Therapy 2 program, a model incorporating results of GEP and amplification of chromosome 1q21 (amp1q21) represented the most powerful predictor of 3-year OS.[15] The 3-year survival was 16% for patients with both of these characteristics, 35% for those with one, and 49% for those with none. Although GEP is still considered investigational in MM, additional studies will most likely refine the technique so that it can be more incorporated into the prognostic and therapeutic management of patients.

Management Principles

Figure 1 summarizes the general approach to MM treatment advocated by the NCCN. Individuals with smoldering or early-stage, asymptomatic MM undergo observation without therapy, although the use of bisphosphonates in patients with significant osteopenia or early bone disease is reasonable to consider, and participation in clinical trials addressing this issue is encouraged. The initial management of individuals with symptomatic disease is determined by eligibility for high-dose therapy and autologous stem cell transplantation (ASCT). Eligibility for ASCT is established primarily based on age and comorbidity, with an age limit of 65 to 70 years as a somewhat arbitrary cutoff for eligibility. Using the procedure for older individuals who are otherwise fit can be considered at the discretion of the treating physician. Comorbid cardiovascular, pulmonary,

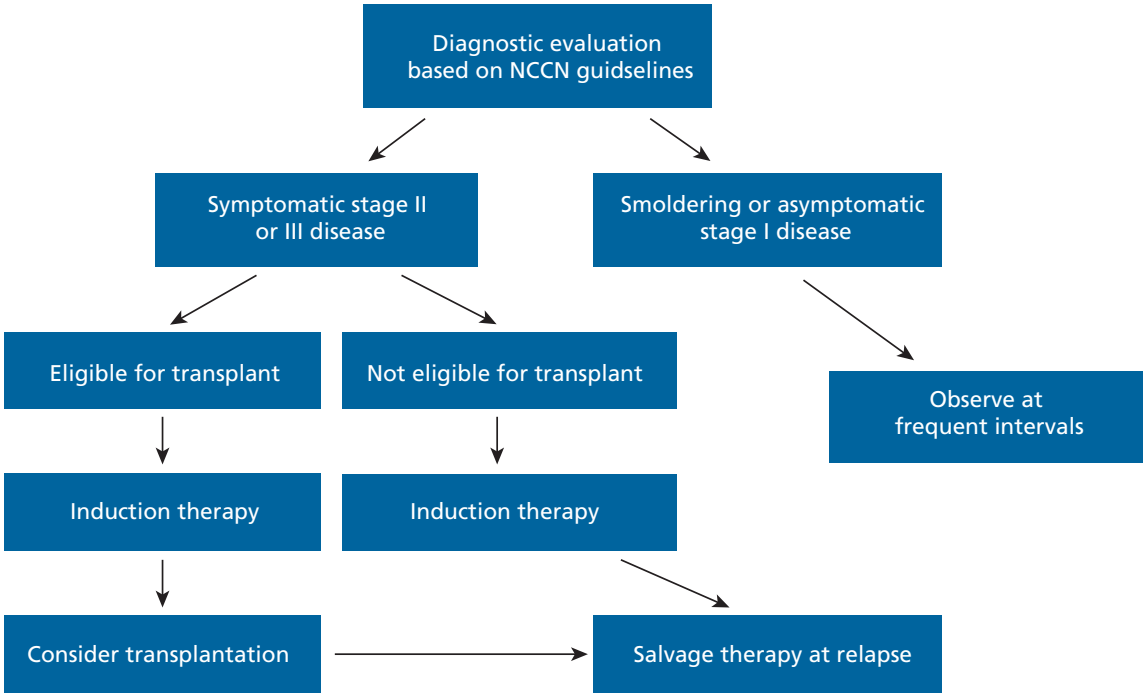

Figure 1 Approach to treatment of multiple myeloma

hepatic, and renal disease should be considered carefully when assessing patient fitness for ASCT. Impaired renal function (creatinine clearance > 2 mg/mL) when the procedure is performed has been associated with inferior survival.[16]

Before novel therapies were developed, patients ineligible for ASCT typically underwent induction therapy with oral melphalan and prednisone, a regimen associated with an overall response rate of approximately 50%.[17] A standard regimen for patients eligible for ASCT, however, involved vincristine, doxorubicin, and dexamethasone (VAD), with overall and complete response (CR) rates up to 84% and 27%, respectively, in patients who underwent VAD followed by ASCT.[18] Relapsed disease was managed with regimens such as high-dose dexamethasone;[19,20] VAD;[21–23] vincristine, melphalan, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, and prednisone (VMPC/VBAP);[24] and doxorubicin, vincristine, dexamethasone, etoposide, and cyclophosphamide (CEVAD).[25]

The introduction of thalidomide, lenalidomide, and bortezomib in MM has dramatically changed the management of these patients. As reflected in the current NCCN guidelines, these agents are now used as first-line therapy for individuals with relapsed MM and for transplant-eligible and -ineligible patients with newly diagnosed disease. In addition, maintenance therapy after ASCT can be considered in these patients. Data supporting the role of thalidomide, lenalidomide, and bortezomib in these settings are reviewed later.

Novel Therapies

Thalidomide

Thalidomide-containing regimens can be used as salvage therapy in the setting of relapsed disease, primary induction therapy for transplant and nontransplant candidates, and maintenance therapy after ASCT. Properties of thalidomide that account for its anti-MM activity include inhibition of angiogenesis through effects on vascular endothelial growth factor and basic fibroblast growth factor,[26] enhancement of T cell and natural killer (NK) cell–mediated immunologic response,[27] disruption of MM stromal cell adhesion,[28] and induction of caspase 8–mediated apoptosis.[29]

Relapsed and Refractory MM: Singhal et al.[30] first showed the activity of thalidomide in a phase II trial in which 84 patients with relapsed and relapsed/refractory MM underwent thalidomide monotherapy at doses ranging from 200 to 800 mg daily. This heavily pretreated group, of which 90% underwent prior ASCT and 69% underwent more than one cycle of high-dose therapy, had an overall response rate of 32%. Among 169 patients who ultimately enrolled in this trial, the 2-year event-free and OS rates were 20% and 48%, respectively,[31] with 10-year event-free and OS rates of 6% and 10%.[32] These results were corroborated by other clinical trials involving thalidomide. A systematic review of 42 phase II trials showed an overall response rate of 29% and median OS of 14 months among 1674 patients with relapsed and refractory MM who underwent thalidomide monotherapy.[33]

Newly Diagnosed MM: As several phase III trials have shown, thalidomide in combination with melphalan and prednisone (MPT) is an effective regimen for patients with newly diagnosed MM who are ineligible for ASCT. In one randomized phase III trial, Palumbo et al.[34] compared MPT with melphalan and prednisone (MP) in 255 previously untreated patients aged 60 years or older. Among patients who received MPT, the overall response and near-complete (nCR) plus CR rates were 76% and 27.9%, respectively, compared with 47.6% and 7.2% in those treated with MP. In addition, MPT was superior to MP in 2-year event-free (54% vs. 27%) and 3-year OS (80% vs. 64%).

In another phase III trial, Facon et al.[35] randomized 447 individuals between ages 65 and 75 with previously untreated MM to receive either MP, MPT, or 2 courses of VAD followed by reduced-intensity ASCT using melphalan (mel-ASCT) 100 mg/m^2. A partial response or better was seen in 35% of patients treated with MP, 76% treated with MPT, and 65% treated with VAD followed by mel-ASCT, and CR rates were 2%, 13%, and 18%, respectively. Although response rates in the MPT and VAD followed by mel-ASCT arms were similar, MPT produced superior PFS (27.5 vs. 19.4 months) and median OS (51.6 vs. 38.3 months).

The efficacy of thalidomide and dexamethasone (TD) induction therapy in patients with newly diagnosed MM eligible for transplant has also been shown in several phase III clinical trials. Rajkumar et al.[36] randomized 207 individuals with newly diag-

nosed MM to either dexamethasone alone or TD, with thalidomide 200 mg daily and dexamethasone 40 mg on days 1 to 4, 9 to 12, and 17 to 20. Superior overall response (63% vs. 41%) and CR (4% vs. 0%) rates were achieved in the TD arm compared with the dexamethasone arm. Grade 3 or higher toxicities, including deep vein thrombosis (DVT), rash, neuropathy, and bradycardia, were more common with TD.

In a second, larger phase III trial, Rajkumar et al.[37] randomized 470 patients with MM who were eligible for transplant to treatment with either dexamethasone plus placebo or TD, with thalidomide dose escalated from 50 mg daily at treatment initiation to 200 mg. Combination therapy yielded an overall response rate of 64%, whereas dexamethasone alone produced an overall response rate of 46%. Time to progression (TTP) was significantly longer in patients who received the combination (22.6 vs. 6.5 months). Grade 3 or higher toxicities were more common in the TD arm than those treated with dexamethasone alone (79.5% vs. 64.2%).

Superior response rates achieved with TD induction before ASCT, compared with either induction treatment with dexamethasone alone or VAD, have not necessarily translated into comparable improvements in overall response posttransplant. This discrepancy is illustrated by Macro et al.,[38] who randomized 203 patients with previously untreated MM to either 4 cycles of TD or 3 cycles of VAD induction, followed by high-dose melphalan 200 mg/m^2 and ASCT. Although the rate of very good partial response (VGPR) or better was higher in the TD group before stem cell collection (24.7% vs. 7.3%), this clinical benefit was not sustained. The rates of VGPR or better in the TD and VAD arms 6 months after ASCT were very similar, at 44% and 42%, respectively.

Maintenance Therapy: The role of thalidomide maintenance after ASCT has been evaluated in several randomized trials. In a study by Attal et al.,[39] 597 patients with MM were randomized after induction therapy and ASCT to either observation, pamidronate, or pamidronate plus thalidomide, 400 mg daily. The rates of VGPR or better, 3-year event-free survival, and 4-year OS were significantly better among patients who received pamidronate plus thalidomide than among those in the other treatment groups.

In another study of thalidomide maintenance, Spencer et al.[40] randomized 243 patients with MM who had previously undergone induction therapy followed by stem cell collection, high-dose therapy, and ASCT to either prednisolone maintenance alone (50 mg every other day) or the same dose and schedule of prednisolone plus thalidomide (initial dose 100 mg daily, with an increase to 200 mg daily after 2 weeks if well tolerated). Use of thalidomide maintenance resulted in superior 3-year PFS (42% vs. 23%) and OS (86% vs. 75%). Notably, the rates of survival after disease progression were similar.

Thalidomide has also been assessed as part of the Total Therapy 2 program. In a study by Barlogie et al.,[41] 668 patients with newly diagnosed MM were treated with an extensive regimen involving induction with VAD, DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin), and CAD; tandem ASCT using high-dose melphalan; consolidation with DPACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide); and maintenance with interferon-α and dexamethasone.

In addition to this regimen, study participants were randomized to either placebo or thalidomide as part of induction, consolidation, and maintenance. The incorporation of thalidomide within the treatment regimen resulted in higher rates of CR (62% vs. 43%) and 5-year event-free survival (56% vs. 44%). However, the 5-year OS was equivalent in the treatment groups at 65%, and median survival after relapse was surprisingly shorter in the thalidomide group (1.1 vs. 2.7 years). Longer follow up had determined that among patients with cytogenetic abnormailities, the incorporation of thalidomide with Total Therapy prolonged OS.[42]

Concern raised by results from the Total Therapy 2 experience regarding disease progression after relapse in thalidomide recipients has been corroborated by preliminary results of the Medical Research Council Myeloma IX study from the United Kingdom, in which patients underwent either intensive or nonintensive induction therapy followed by randomization to thalidomide or no maintenance.[43] Although thalidomide maintenance conferred benefit in terms of PFS, this did not translate into an OS advantage. A nonsignificant trend in OS benefit was seen in the group that did not undergo maintenance. Thus, while several studies have demonstrated clinical benefit derived from thalidomide maintenance following ASCT, a degree of caution must be exercised with this practice.

Thalidomide-Associated Toxicities: Because of the severe teratogenic effects associated with thalidomide, access to the drug is restricted in many countries to individuals who participate in the System for Thalidomide Education and Prescription Safety (STEPS) program. Sedation, fatigue, and constipation should be anticipated in patients who receive thalidomide, and these side effects can be cumulative and dose-dependent.[44] Peripheral neuropathy is a dose- and time-dependent toxicity associated with thalidomide,[45] and results from axonal injury and loss of large-diameter myelinated nerve fibers.[46]

The incidence of venous thromboembolism (VTE) in the context of clinical trials with thalidomide plus either dexamethasone or chemotherapy ranges from 3% to 34% among patients with newly diagnosed MM, and from 2% to 15% among those with relapsed and refractory disease.[47] Anticoagulation with either full-dose warfarin targeting an international normalized ratio of 2.0 to 3.0 or a prophylactic dose of low molecular weight heparin is generally preferred for individuals who receive thalidomide in combination with either dexamethasone or chemotherapy,[48] whereas aspirin is appropriate for patients intolerant of or unwilling to undergo anticoagulation.

Other infrequent but important thalidomide-associated toxicities include bradycardia,[49] hypothyroidism,[50] hepatotoxicity,[51] pulmonary hypertension, and skin reactions ranging from a mild macular–papular rash[52] to life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis.[53]

Lenalidomide

Lenalidomide is a thalidomide analogue with the structural backbone of its parent compound modified through elimination of a carbonyl group and addition of an amine. The anti-MM activity of the compound is exerted through several mechanisms, including upregulation of interferon-γ and interleukin (IL)-2 with a resulting increase in NK cell activity, inhibition of angiogenesis, induction of apoptosis, and modulation of MM cells binding to bone marrow stromal cells.[27,54–56] Lenalidomide also modulates bone metabolism, promoting bone formation by potently inhibiting osteoclastogenesis.[57] Lenalidomide-containing regimens are recommended by the NCCN for managing patients with newly diagnosed and relapsed MM.

Relapsed and Refractory MM: In a phase I study in which 27 patients with relapsed and refractory MM (median of 3 prior therapies) received escalating doses of lenalidomide ranging from 5 to 50 mg daily, the rate of minimal response or better was 70%.[58] All 13 patients receiving the highest dose level (50 mg/d) developed grade 3 myelosuppression after one cycle of treatment, whereas the dose of 25 mg daily was well tolerated and therefore selected as the maximal tolerated dose (MTD).

In a subsequent randomized phase II study, 102 patients with relapsed MM received lenalidomide at a dose of either 30 mg once daily or 15 mg twice daily,[59] with the daily dose proving to be better tolerated. The overall response rate (partial response or better) was 25%, and the addition of dexamethasone after 2 cycles for progressive or stable disease led to additional response in 29% of those treated with corticosteroid.

These studies provided the platform for 2 large, randomized phase III clinical trials in relapsed MM: the MM-009 North American study and MM-010 European/Israeli/Australian study.[60,61] Study participants in MM-009 and -010 were randomized to either placebo or 25 mg of lenalidomide on days 1 through 21 of each 28-day cycle. Dexamethasone, 40 mg, was administered to both treatment groups on days 1 to 4, 9 to 12, and 17 to 20 during the first 4 cycles, and only on days 1 to 4 thereafter. Lenalidomide and dexamethasone produced superior overall response rates in both MM-009 (61% vs. 19.9%) and MM-010 (60% vs. 24%). Median TTP, the primary end point of the trial, was significantly longer in the MM-009 (11.1 vs. 4.7 months) and MM-010 (11.3 vs. 4.7 months) studies.

Subgroup analysis of MM-009 and MM-010 showed that, compared with dexamethasone alone, lenalidomide and dexamethasone conferred a better overall response rate, TTP, and PFS, regardless of prior thalidomide exposure.[62] However, an OS benefit was observed in this subgroup analysis with lenalidomide and dexamethasone only in patients who had no prior thalidomide exposure. In addition, more toxicity was noted in patients who had been previously exposed to thalidomide, although overall lenalidomide-based therapy was well tolerated, apart from a high rate of DVT seen with the combination regimen.

More recent early-phase clinical trials suggest that lenalidomide can also be successfully combined with alkylating agents and anthracyclines in the set-

ting of relapsed and refractory MM. For example, in a phase I/II clinical trial, Knop et al.[63] administered lenalidomide, doxorubicin, and dexamethasone (RAD) to 69 individuals with relapsed and refractory MM, 77% of whom had undergone 2 or more previous lines of therapy. Pegfilgrastim was administered at the highest dose level, which included lenalidomide, 25 mg, on days 1 to 21, doxorubicin, 9 mg/m^2, on days 1 to 4, and dexamethasone, 40 mg, on days 1 to 4 and 17 to 20 of each 28-day cycle. The MTD was not reached in this study. The overall response rate was 73%, whereas 74% of patients treated at the highest dose level experienced a VGPR or better.

Meanwhile, Morgan et al.[64] used lenalidomide, 25 mg, on days 1 to 21, cyclophosphamide, 500 mg, on days 1, 8, 15, and 21, and dexamethasone, 40 mg, on days 1 to 4 and 12 to 15 (RCD) in a phase II study involving 21 patients with relapsed and refractory disease. The combination yielded an overall response rate of 65%, including a 5% CR and 15% VGPR, but toxicities were important, including myelosuppression and thromboembolism.

Although the 2009 NCCN guidelines do not recommend regimens combining lenalidomide with either cyclophosphamide or doxorubicin as therapies for relapsed and refractory MM, they are still promising, and the results of later-phase clinical trials are anticipated with interest.

Newly Diagnosed MM: Lenalidomide-based therapy has also been applied successfully to the management of individuals with newly diagnosed MM. In a phase II study, Lacy et al.[65] treated 34 individuals with previously untreated MM using lenalidomide, 25 mg, days 1 to 21, and dexamethasone, 40 mg, days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle. After 4 cycles of induction, patients could continue lenalidomide and dexamethasone therapy, undergo ASCT, or be observed without undergoing therapy. The overall response rate was 91%, with partial response, VGPR, and CR rates of 35%, 38%, and 18%, respectively. The 2-year PFS for patients who underwent ASCT and those who remained on lenalidomide and dexamethasone were 83% and 59%, respectively. The 3-year OS for those who underwent ASCT was 92% and 85% for those who remained on lenalidomide and dexamethasone.

In the large phase III ECOG E4A03 trial, Rajkumar et al.[66] randomized 445 patients with newly diagnosed MM to receive lenalidomide, 25 mg, on days 1 to 21 and either high-dose dexamethasone (RD, 40 mg/d, days 1–4, 9–12, and 17–20) or low-dose dexamethasone (Rd, 40 mg, days 1, 8, 15, and 22). In preliminary analysis, RD was superior to Rd with respect to overall response (82% vs. 70%). However, Rd yielded superior OS compared with RD: 96% versus 88% at 1 year and 87% versus 75% at 2 years. Grade 3 or greater toxicity occurred in 50% of patients treated with RD, as opposed to 30% in those who received Rd, which partly explains the inferior outcomes seen with the higher-dose dexamethasone arm.

Lenalidomide-Associated Toxicities: Although the teratogenic effects of lenalidomide in humans are unknown, access to the drug is restricted to individuals who participate in the RevAssist program, developed by the manufacturer, Celgene Corporation, to prevent fetal exposure to lenalidomide and thus minimize the risk for birth defects. During the first year of lenalidomide's availability in the United States, 15,584 patients registered in the RevAssist program and no pregnancies occurred in female patients or female partners of male patients.[67] Unlike thalidomide, lenalidomide is rarely associated with peripheral neuropathy. Myelosuppression was the most common high-grade toxicity in MM-009 and -010 clinical trials.[60,61] Although lenalidomide as a single agent has not been associated with a markedly increased risk for VTE,[68] the lenalidomide and dexamethasone doublet was associated with VTE rates of 14.7% and 8.5% in MM-009 and -010 studies, respectively.[60,61] A rash, which may be morbilliform, urticarial, dermatitic, or acneiform, develops in up to 30% of patients who receive lenalidomide.[69] Other rare toxicities reported in patients undergoing lenalidomide-based therapy include hepatotoxicity[70] and hypersensitivity pneumonitis.[71]

Concern has been raised regarding the impact of lenalidomide on stem cell collection before ASCT. In a retrospective analysis, Kumar et al.[72] noted a decrease in the total number of CD34+ stem cells collected, average daily stem cell collection, and stem cells collected on day 1 of apheresis, and an increased number of apheresis cycles in patients for whom granulocyte colony-stimulating factor was used for mobilization after induction with lenalidomide plus dexamethasone compared with induction with VAD, TD, or dexamethasone alone. Increasing age and longer courses of induction therapy with

lenalidomide and dexamethasone were associated with a lower stem cell yield.

Meanwhile, Mazumder et al.[73] found that among a group of patients with MM who underwent mobilization after lenalidomide and dexamethasone, 12 (43%) did not have sufficient stem cell collection for a single ASCT. Thus, although further study of this issue is necessary, caution should be used when treating candidates for ASCT with lenalidomide and dexamethasone or other lenalidomide-containing induction regimens, particularly in older patients and those for whom a longer course of induction therapy is anticipated.

Bortezomib

Bortezomib is a boronic acid dipeptide small molecule that reversibly inhibits the chymotrypsin-like activity of the 20S proteasome. The agent's anti-MM activity derives from several mechanisms, including inhibition of NK-kB, induction of caspase 8/9–mediated apoptosis, cleavage of DNA repair enzymes, and disruption of IL-6–induced activation of the ERK, STAT3, and AKT pathways.[74–78] In addition, bortezomib influences bone metabolism by inhibiting osteoclastogenesis and promoting osteoblast differentiation and proliferation.[79,80]

Relapsed and Refractory MM: Phase I and II studies involving patients with relapsed MM showed manageable treatment-associated toxicity and significant activity in this setting.[81–83] Moreover, response to therapy seemed to be independent of adverse features, such as abnormal cytogenetics, number and type of prior therapies, and light chain disease.[84]

These studies were followed by a phase III study in which 669 patients with relapsed MM were randomized to receive either 1) bortezomib, 1.3 mg/m^2, on days 1, 4, 8, and 11 of each 21-day cycle for eight 3-week cycles, followed by treatment on days 1, 8, 15, and 22 for 5-week cycles, or 2) dexamethasone, 40 mg, on days 1 through 4, 9 through 12, 17 through 20 for four 5-week cycles, followed by treatment on days 1 through 4 for five 4-week cycles.[85] Bortezomib was superior to high-dose dexamethasone with respect to rates of overall response (38% vs. 18%), CR (6% vs. 1%), median TTP (6.22 vs. 3.49 months), and 1-year OS (80% vs. 66%). Grade 3/4 treatment-related toxicities included thrombocytopenia (26%), neutropenia (14%), anemia (10%), peripheral neuropathy (7%), and diarrhea (7%).

With extended follow-up of study participants, the overall response and CR rates among patients treated with bortezomib increased to 43% and 9%.[86] Median OS was 29.8 months in the bortezomib arm versus 23.7 months in the dexamethasone arm, despite crossover in more than 60% of patients. Furthermore, activity was seen in patients with adverse features, advanced age, and poor-risk cytogenetics.[87]

Clinical trials have shown the effectiveness of regimens combining bortezomib with both corticosteroids and anthracyclines. In 2 phase II studies of bortezomib in the setting of relapsed MM, patients with progressive disease after 2 cycles or stable disease after 4 cycles could receive oral dexamethasone, 20 mg, on the day of and day after bortezomib.[82,83] The addition of dexamethasone led to significant responses among patients with either stable or progressive disease on bortezomib.

In a phase III trial by Orlowski et al.,[88] patients with relapsed MM, 66% of whom had undergone 2 or more prior lines of therapy, received either bortezomib, 1.3 mg/m^2, on days 1, 4, 8, and 11 of each 21-day cycle or the same regimen of bortezomib in combination with liposomal doxorubicin pegylated liposomal doxorubicin 30 mg/m^2 on day 4. The combination was superior to bortezomib alone in terms of median TTP (9.3 vs. 6.5 months) and 15-month OS (76% vs. 65%). Although grade 3/4 toxicities, such as anorexia, vomiting, thrombocytopenia, neutropenia, and hand–foot syndrome, occurred more frequently with the doublet, cardiac toxicity was only minimally increased with the combination, and rates of peripheral neuropathy were equivalent.

Newly Diagnosed MM: Bortezomib in combination with melphalan and prednisone is an effective regimen for patients with newly diagnosed MM who are ineligible for ASCT. In a phase III trial by San Miguel et al.,[89] 682 patients ineligible for ASCT with previously untreated MM were randomized to either bortezomib plus melphalan and prednisone (VMP) or MP alone. All patients received melphalan, 9 mg/m^2, and prednisone, 60 mg/m^2, days 1 through 4 of each 6-week cycle, whereas bortezomib was administered in the combination arm at 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 through 4 and on days 1, 8, 22, and 29 during cycles 5 through 9. VMP was superior to MP regarding the study's primary end point of TTP (24 vs. 16.6 months) and secondary end points of CR rate (30% vs. 4%) and duration of response (19.9 vs. 13.1 months). The

hazard ratio for survival also favored VMP over MP (0.61). Grade 3 toxicities occurred more frequently with VMP than MP (53% vs. 44%), whereas grade 4 toxicities were equivalent (28% vs. 27%). Within the VMP arm, 13% of patients experienced grade 3 peripheral neuropathy.

For patients with newly diagnosed MM who are eligible for transplant, bortezomib and dexamethasone (VD) and bortezomib plus doxorubicin and dexamethasone (PAD) are recommended by the NCCN based on data from ongoing phase III studies. In a study by Harousseau et al.,[90] 480 patients with newly diagnosed MM were randomized to induction therapy with either VAD or VD. Study participants then underwent a second randomization to 2 cycles of DCEP consolidation or not before ASCT. Preliminary analysis showed that VD was superior to VAD induction with respect to rates of VGPR or better (46.7% vs. 18.6%) and CR/nCR (21.3% vs. 8.3%), even among patients with advanced ISS score and del(13). Clinical benefit associated with VD persisted post-ASCT with respect to rates of CR/nCR (40.8% vs. 28.8%) and VGPR or better (71.8% vs. 51%). Response rates were not improved in either treatment group by DCEP consolidation. Although therapy-related peripheral neuropathy occurred more frequently with VD induction therapy, the overall rate of treatment-associated toxicities was equivalent. Stem cell collection was successful in 97% of study participants who received VD and 99% of those who received VAD.

An ongoing phase III study by Sonneveld et al.[91] has shown that PAD is also effective as induction therapy for individuals with newly diagnosed MM. This trial randomized 883 patients eligible for transplant to either VAD or PAD followed by stem cell mobilization and either single or tandem ASCT. Patients in the VAD group then underwent maintenance therapy with thalidomide, 50 mg daily, whereas those in the PAD arm received bortezomib, 1.3 mg/m^2, every other week as maintenance. In a preliminary analysis, PAD induction was superior to VAD with respect to rates of overall response (80% vs. 64%), VGPR or better (41% vs. 17%), and CR (5% vs. 0%). The benefit of PAD was also observed post-ASCT, with superior overall response (92% vs. 77%) and CR (15% vs. 4%) rates. In the PAD arm, bortezomib maintenance improved responses further, with an increase in the CR/nCR rate from 23% to 35%.

Bortezomib-Associated Toxicities: Peripheral neuropathy, thrombocytopenia, and gastrointestinal symptoms are important side effects associated with bortezomib use. The incidence of bortezomib-associated peripheral neuropathy seems to be cumulative, with its incidence peaking at a dose of approximately 30 mg/m^2.[92] In most cases, bortezomib-associated peripheral neuropathy is reversible with interruption of therapy or dose-modification.[92–94] Thrombocytopenia occurring in the context of bortezomib therapy typically follows a cyclical, biphasic pattern, with a decline in the platelet count during the 2-week treatment period followed by recovery during the rest period.[95]

Gastrointestinal side effects observed with bortezomib include diarrhea, nausea and emesis, constipation, anorexia, and abdominal pain. Attentive symptom-directed management using stool softeners, laxatives, antidiarrheals, antiemetics, and either proton-pump inhibitors or H_2-recepteor blockers, as appropriate, is recommended. Bortezomib is associated with an increased risk for herpes zoster virus reactivation, and therefore antiviral prophylaxis should be considered in patients who have no contraindications to such therapy. Rare instances of lung injury, including bronchiolitis obliterans with organizing pneumonia,[96] pulmonary fibrosis,[97] and diffuse alveolar hemorrhage[98] have been reported in patients receiving bortezomib, but were reversible with the use of high-dose steroids.

Novel Agents in Combination

Given that thalidomide, lenalidomide, and bortezomib exert antimyeloma activity through unique pathways, interest in combination regimens involving these agents has been considerable. Several of these combination regimens are included in the 2009 NCCN Multiple Myeloma Guidelines based on compelling evidence from clinical trials. Bortezomib, thalidomide, and dexamethasone (VTD), for example, is an effective regimen for patients with previously untreated MM who are eligible for ASCT.

In an ongoing phase III study, Cavo et al.[99] randomized 480 patients with newly diagnosed MM who were eligible for transplant to VTD or TD. Patients in the TD group received thalidomide, 200 mg daily, on days 1 through 63 with dexamethasone, 40 mg daily, on days 1 to 4 and 9 to 12 of each 21-day cycle,

whereas those in the VTD arm received the same dose and schedule of thalidomide, with bortezomib, 1.3 mg/m^2, given on days 1, 4, 8, and 11 of each 21-day cycle and dexamethasone, 40 mg, on the day of and day after each dose of bortezomib. Preliminary analysis showed the superiority of VTD to TD with respect to rates of overall response (92% vs. 78.5%), CR/nCR (33% vs. 12%), and VGPR or better (61% vs. 30%).

Although the combination of bortezomib and thalidomide prompted concern for peripheral neuropathy, the toxicity profile associated with this regimen has been manageable. Although the rate of grade 3 or greater peripheral neuropathy was moderately higher in the VTD arm (9% vs. 2.5%), the overall rate of serious adverse events was similar in the treatment arms, and few patients discontinued therapy because of treatment-related toxicity. A sufficient number of stem cells for up to 2 ASCTs were collected in 91% of patients in the VTD group and 87% in the TD arm. Among patients who underwent ASCT, those treated with VTD experienced higher posttransplant rates of VGPR or better (75% vs. 53%), CR/nCR (54% vs. 29%), and CR (41% vs. 20%). After 15 months of follow-up, PFS for VTD was superior to TD (93% vs. 86), whereas 20-month OS was equivalent.

Bortezomib in combination with lenalidomide and dexamethasone (RVD) was also proven to be highly effective in treating newly diagnosed and relapsed MM. In vitro modeling provided evidence of synergistic tumoricidal activity between bortezomib and lenalidomide and provided the rationale for this combination.[100]

In a phase II study, 64 patients with relapsed and refractory MM who had received 1 to 3 prior lines of therapy were treated with bortezomib, 1.0 mg/m^2, days 1, 4, 8, and 11; lenalidomide, 15 mg, days 1 to 14; and dexamethasone, 40 mg (cycles 1–4) or 20 mg (cycles 5–8), on the day of and after bortezomib administration for up to eight 21-day cycles.[101] The rate of minimal response or better in this study is 86%, with 24% of participants experiencing a CR/nCR and 67% a partial response or better. Patients whose MM responded to therapy experienced a median duration of remission of 21 weeks. Response rates in this study were equivalent among patients with standard and high-risk disease features, including advanced ISS stage and cytogenetic abnormalities. Toxicities observed in association with RVD have included grade 1 to 2 myelosuppression and only 2 cases of DVT, with minimal significant peripheral neuropathy.

The efficacy of RVD in the upfront setting was evaluated in an ongoing phase I/II study involving 68 patients eligible for transplant with previously untreated MM. Among study participants, 33 underwent therapy as part of a phase I dose-escalation component and 35 as part of a phase II portion using the MTD of lenalidomide, 25 mg, and bortezomib, 1.3 mg/m^2, along with dexamethasone on the day of and day after bortezomib at a dose of 20 mg.[102,103] Among patients treated at the MTD, the overall response rate was 100%, whereas the rates of VGPR or better and CR/nCR have been 74% and 44%, respectively. Rates of response were not affected by adverse prognostic features, such as del(13) and t(4;14). The toxicity profile has also been favorable, with low rates of DVT/pulmonary embolism (5%) and grade 3 or greater peripheral neuropathy (3%). Data from long-term follow-up are awaited with interest, and this regimen is now being studied in large, randomized phase III trials.

Choice of Therapy

As a result of the successful clinical development of multiple novel agents and combination regimens, clinicians can now choose from various treatment options to manage patients with newly diagnosed and relapsed MM. In the upfront setting, age, suitability for ASCT, patient preference regarding oral versus intravenous drug administration, comorbid conditions, and risk stratification based on ISS and cytogenetic findings are important determinants of initial therapy. Lenalidomide- or thalidomide-based therapies are used for patients who prefer or require oral therapy.

Bortezomib-containing regimens are favored for patients with high-risk cytogenetic abnormalities, because the agent was consistently shown to overcome the poor prognosis associated with these findings.[87,90] Bortezomib-based induction therapy is also effective in patients with renal dysfunction, which is noted in 20% to 40% of individuals with newly diagnosed MM.[104] The anti-MM activity of bortezomib is preserved in patients with renal failure, and a significant number of patients experience improvements in renal function after therapy.[105,106]

Decisions concerning 2- versus 3-drug regimens are influenced by individualized treatment goals. Three-drug regimens, such as VTD and RVD, produce higher overall response and CR rates, with manageable side effect profiles. Ongoing and forthcoming clinical trials will determine whether these regimens significantly prolong survival.

In the context of relapsed MM, prior therapy and duration of response to prior therapy influence decisions on appropriate treatment. An IMiD-containing regimen is a logical choice for patients who are refractory to or experience relapse after a short progression-free interval with bortezomib-based therapy. Similarly, bortezomib-based therapy is indicated for patients who are refractory to or experience a short progression-free interval with IMiD treatment. However, relapse does not indicate resistance to previously used agents. When a durable response to a particular agent or combination occurs, retreatment at relapse may be appropriate. Moreover, refractory disease can sometimes be treated with a particular agent to which resistance has developed if the agent is used in conjunction with other compounds that produce synergistic anti-MM effects. Toxicities incurred during prior therapies are also considered when choosing agents at relapse. For example, lenalidomide is preferred for patients who previously developed grade 2 with pain or grade 3/4 peripheral neuropathy with either bortezomib or thalidomide.

Future Directions and Conclusions

As reflected by the current NCCN Multiple Myeloma Guidelines, the novel agents thalidomide, lenalidomide, and bortezomib are now first-line options for patients with both newly diagnosed and relapsed MM, and provide a paradigm of drug development in MM.[107] Significant progress has been made in the management MM due to the development of these agents. However, further improvement is necessary, as MM remains incurable and represents a source of substantial morbidity for individuals affected by this disease. In this respect, it is expected that ongoing clinical research will result in the further development of active, well tolerated combination regimens and will at the same time inform the appropriate use of such regimens in conjunction with other treatment modalities such as ASCT. Moreover, it is anticipated that the emergence of several new compounds used either alone or in combination with either dexamethasone, bortezomib, and/or lenalidomide currently undergoing evaluation in MM will broaden the repertoire of MM therapies still further and thus improve outcomes for patients with this disease.

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