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THE EVOLVING SPECTRUM OF COMBINATION TREATMENT STRATEGIES IN MULTIPLE MYELOMA

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Introduction

As a result of important advances in the treatment of **MM**, the outlook for patients with this disease has improved significantly in recent years. Specifically, the introduction of novel agents, including thalidomide, lenalidomide, and bortezomib, has had a favorable impact on prognosis. Although **MM** remains incurable, the use of novel therapies has increased **OS** from less than 2 years to approximately 5 years and to between 7 and 10 years for certain subsets of patients.¹⁻³ Regimens incorporating the novel agents have produced combined rates of **CR** and **VGPR** of 75% or better in the treatment of newly diagnosed **MM**, with **PR** or better among close to 95% of evaluable patients depending on the regimen.²⁻⁶ Given the known association between survival and deep responses to therapy, it thus appears that the robust anti-**MM** activity of novel agents accounts for improvements in patient outcomes observed in recent years.

In spite of such progress, important challenges remain. Primary drug resistance is still observed in a subset of patients,³ and nearly all disease eventually relapses, including patients who initially achieve **CR**.² In addition, toxicities related to the therapeutic agents themselves can occur and must be managed carefully. It may be that in the future, genomic profiling will allow for the selection of treatment regimens that are most likely to benefit each patient on the basis of the individual's gene-expression characteristics.⁷ It is also likely that alterations in both dose and schedule of chemotherapeutic regimens incorporating novel agents will reduce toxicities. At present, decisions regarding therapeutic regimens are made based on features of the underlying disease and comorbid conditions such as renal dysfunction, cytopenias, and **PN**.

An increasing number of options are now available for **MM** therapy, and a review of them in entirety is beyond the scope of this paper. This review focuses on regimens incorporating novel agents in the level 1 category of the 2010 **NCCN** Clinical Practice Guidelines (**Table 1**).⁸

Table 1. NCCN Categories⁸

Category	Basis
1	High-level evidence (eg, randomized controlled trials) and uniform NCCN consensus
2A	Lower-level evidence and uniform NCCN consensus
2B	Lower-level evidence and nonuniform NCCN opinions but no major disagreement
3	Any level of evidence but with major NCCN disagreement

FACTORS THAT INFLUENCE TREATMENT DECISIONS

Treatment decisions in **MM** are increasingly tailored to the individual patient and are typically based on a number of clinical factors. Such factors include age, disease stage, type and extent of end-organ injury, cytogenetic findings, and other specific features of the disease such as degree of urinary light-chain excretion,

percentage of circulating plasma cells, and the plasma cell labeling index, if available. Choice of therapy is also influenced by eligibility for **SCT**, as transplant-eligible patients have typically undergone induction therapy followed by either single or tandem **SCT**, whereas patients ineligible for transplantation are treated with standard induction regimens alone (**Tables 2 and 3**).⁸⁻¹⁰

Encouraging results obtained with the incorporation of novel agents in **MM** therapy have, however, changed the paradigm by which treatment decisions are made. High response rates now obtained with frontline therapy incorporating thalidomide, lenalidomide, and bortezomib may modify the manner in which high-dose therapy is used in the care of patients with **MM**. For example, given the increasing number of patients who achieve **CR** with novel frontline therapies, **SCT** may be deferred until the time of relapse. Similarly, high response rates to second-line or salvage therapy may influence decisions regarding **SCT**.¹¹

Choice of treatment regimen is also influenced by the goals of therapy. In some instances, an intensive induction regimen is warranted, with the goal being a long and sustained **CR**, whereas in others a less intensive approach is appropriate, with the goal being long-term disease control. The dichotomy between these approaches was captured in a 2008 commentary by Vincent Rajkumar, MD, of the Mayo Clinic, in which the merits of an “operational cure” (defined as a sustained **CR** for a prolonged period) versus the more modest goal of long-term disease control were considered.¹²

Table 2. Primary Therapy for Patients Not Eligible for SCT⁸⁻¹⁰

Regimen	NCCN Category	Change in Use Patterns
Lenalidomide/low-dose dexamethasone	1	↑
Melphalan/prednisone/bortezomib	1	n/c
Melphalan/prednisone/thalidomide	1	n/c
Melphalan/prednisone	2A	n/c
Lenalidomide/bortezomib/low-dose dexamethasone	2A	↑
Liposomal doxorubicin/vincristine/dexamethasone*	2B	n/c
Thalidomide/dexamethasone*	2B	↓
Vincristine/doxorubicin/dexamethasone*	2B	↓↓

*High-dose dexamethasone as a single agent may have a role in stabilizing patients prior to additional therapy. In combination, lower doses can be used; VAD has little or no role given the toxicity profile of vincristine in particular.

Table 3. Primary Induction Therapy for Transplant-Eligible Patients⁸⁻¹⁰

Regimen	NCCN Category	Change in Use Patterns*
Bortezomib/dexamethasone	1	↑
Bortezomib/doxorubicin/dexamethasone	1	↑
Bortezomib/thalidomide/dexamethasone	1	↑
Lenalidomide/low-dose dexamethasone	1	↑
Lenalidomide/bortezomib/low-dose dexamethasone	2A	↑
Dexamethasone	2B	↓
Liposomal doxorubicin/vincristine/dexamethasone	2B	↓
Thalidomide/dexamethasone	2A	↓

*Bolded arrows represent significant changes in utilization based on recent data from multiple studies, including randomized, controlled trials.

OVERVIEW OF NOVEL AGENTS

The mechanisms of action of the novel agents include direct anti-**MM** activity as well as disruption of interactions between tumor cells and the bone marrow microenvironment.¹³⁻¹⁵

Thalidomide

Thalidomide (Thalomid[®]; Celgene Corporation) is indicated for the treatment of newly diagnosed and relapsed **MM**. In the setting of newly diagnosed disease, thalidomide has been used both for patients eligible for **ASCT** and for those who are ineligible. Thalidomide can also be used in maintenance therapy following

SCT. Thalidomide exerts its anti-**MM** activity through various mechanisms, including modulation of the immune system, induction of apoptosis, inhibition of angiogenesis, and disruption of specific cytokine pathways, as well as disruption of **MM** cell growth and adhesion in the bone marrow microenvironment.^{11,15}

Thalidomide produces a number of important treatment-related toxicities, particularly with increasing dosage and duration of therapy.¹⁶ **PN** occurs in up to 80% of patients with prolonged use,¹⁷ although immediate dose reduction or discontinuation of therapy when symptoms develop can decrease the severity of neuropathy.¹⁸ Thalidomide is associated with an increased incidence of **DVT**, particularly when it is used in conjunction with dexamethasone or chemotherapy.¹⁶ Prophylactic anticoagulation is therefore recommended with thalidomide-based therapy⁸; the goal of thromboprophylaxis is to reduce the rate of thromboembolism to less than 5 to 10%.¹⁸

Thalidomide dosage reductions have been used in an effort to limit adverse effects. Although this approach has raised concerns regarding therapeutic efficacy, retrospective analyses indicate that dosages as low as 50 to 100 mg/day are effective and better tolerated than dosages of 400 to 800 mg/day.¹⁹ Intermittent, as opposed to continuous, administration of thalidomide during induction may also reduce toxicity associated with the drug.²⁰ Thalidomide dosage adjustment is not required for patients with renal impairment or for those on dialysis, although lower dosages (with careful monitoring) are typically used in this setting.¹⁶

Bortezomib

Bortezomib (Velcade[®]; Millennium Pharmaceuticals, Inc., Cambridge, MA, and Johnson & Johnson Pharmaceuticals, Research and Development, L.L.C., Raritan, NJ), a first-in-class proteasome inhibitor, was initially approved in the United States and the European Union for the treatment of **MM** in patients who had received at least one prior therapy and is now also approved as frontline treatment of newly diagnosed **MM**. The new indication was based on results of the Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone (VISTA) trial, which demonstrated that when bortezomib was added to standard therapy (melphalan and prednisone), it significantly improved **TTP** and **OS**.²¹ Encouraging results with bortezomib have also been observed in the setting of community oncology practices; a prospective study of data from office-based hematologists in Germany found that the response rates and adverse events observed with bortezomib in this setting were consistent with results of large-scale clinical trials.²²

In addition to its direct anti-**MM** effect, bortezomib has a protective effect on bone in **MM** based on its ability to inhibit osteoclast formation and stimulate osteoblast activity. It is thus thought that combinations of bortezomib with other agents that stimulate bone formation or block bone resorption may prove to be beneficial for patients with extensive bone involvement.²³

An important feature of bortezomib is its efficacy for patients with adverse cytogenetic features, such as 13q- and 17p deletions.²⁴⁻²⁷ Bortezomib is also safe and effective for patients with renal insufficiency.²⁸ For example, in a recent study of 20 patients with **MM** and renal failure (serum creatinine ≥ 2 mg/dL at baseline), treatment with a bortezomib-containing combination reversed renal failure in 40% of patients over a median interval of 17 days. A 50% decrease in serum creatinine was achieved by 50% overall, and some decrease in serum creatinine level was seen in 85%. Importantly, of 5 patients initially on dialysis, 1 became dialysis independent after the second cycle of treatment.²⁹

Bortezomib is generally well tolerated, although it has been associated with a number of important toxicities. **PN** is the most important treatment-associated toxicity. In clinical trials, the rate of bortezomib-associated **PN** has been approximately 35% to 40%,³⁰ with severe neuropathy occurring in 9% to 14% of patients.³¹ **PN** is reversible in most patients and can be mitigated through proactive dose reduction, treatment interruption, or the use of a weekly schedule.³² Bortezomib-associated **PN** is dose dependent, occurring most frequently at a cumulative dose of 30 mg/m².³³ The risk of **DVT** with bortezomib is very low; thus, prophylactic anticoagulation is not required in conjunction with its use, and it may reduce the thrombotic risk of certain combinations, such as with thalidomide. Treatment-associated thrombocytopenia and neutropenia are common but tend to be transient, resolving during the treatment-free period at the conclusion of each cycle of therapy.^{34,35} Importantly, prophylaxis against herpes zoster with acyclovir or an alternative antiviral agent is recommended along with bortezomib treatment, as reactivation of herpes zoster virus in the form of shingles can occur if preventive therapy is not used.⁸

Lenalidomide

Lenalidomide (Revlimid[®]; Celgene Corporation) is a more potent analog of thalidomide with a toxicity profile that is distinct from that of its parent compound. It is an oral immunomodulatory drug that has broad pleiotropic anti-MM activities, including induction of apoptosis, inhibition of angiogenesis, immunomodulatory effects (such as activation of T cells and natural killer cells), and cadherin modulation of cytokinesis.³⁶ In combination with dexamethasone, lenalidomide has been approved for patients with relapsed and refractory MM. It has been studied extensively as induction therapy and also shows promise as maintenance therapy.⁸

A large North American phase III study of lenalidomide plus dexamethasone demonstrated the efficacy of the combination in relapsed/refractory disease.³⁷ Additionally, a phase III study comparing lenalidomide/high-dose dexamethasone (RD) with lenalidomide/low-dose dexamethasone (Rd) showed the anti-MM activity of these regimens among patients with newly diagnosed MM. In this study, RD yielded higher response rates, but an increased rate of significant treatment-related toxicities such as venous thromboembolic events and infection in this treatment arm translated to lower OS. Therefore, Rd is the preferred combination.³⁸

Post-SCT lenalidomide maintenance is an area of continuing study that has been associated with encouraging results to date. An ongoing phase III study comparing methylprednisolone alone, methylprednisolone/lenalidomide, and this combination followed by lenalidomide maintenance has had promising results with the latter regimen.³⁹ Like bortezomib, lenalidomide has been shown to target specific key factors in osteoclastogenesis and thereby has the potential to diminish osteolytic bone disease in MM.⁴⁰

Important toxicities associated with lenalidomide treatment include neutropenia and thrombocytopenia, which may necessitate dose reduction, and thromboembolic disease, including pulmonary embolism.⁴¹ The incidence of DVT is low with lenalidomide alone and in combination with low-dose dexamethasone but markedly increases along with other therapy-associated toxicities when lenalidomide is given in conjunction with high-dose dexamethasone.^{36,38} As a result of the suppressive effect of lenalidomide on stem cells, it is also recommended that patients being prepared for ASCT undergo stem cell collection within 6 months of lenalidomide therapy initiation.^{8,42} Specifically, lenalidomide decreases the yield of CD34+ stem cells with prolonged exposure, although it has become clear that mobilization is almost always successful when an adequate treatment break is allowed following lenalidomide therapy and mobilization is undertaken with use of both cyclophosphamide and filgrastim or plerixafor.⁴²

Combination Regimens

The clinical efficacy of thalidomide, bortezomib, and lenalidomide in MM as well as synergy demonstrated preclinically has sparked interest in combination regimens involving these agents.

Bortezomib/thalidomide/dexamethasone, for example, is an effective regimen for patients with previously untreated MM who are eligible for ASCT. In an ongoing phase III study involving patients with previously untreated MM, this regimen has been superior to thalidomide/dexamethasone with respect to rates of OR, CR/nCR, and VGPR, and rates of treatment-associated PN have been manageable.⁴³

Bortezomib/lenalidomide/dexamethasone has proven to be highly effective in the treatment of both relapsed and refractory as well as newly diagnosed MM.^{4,44} In the upfront setting, treatment at the maximum tolerated dose of lenalidomide (25 mg) and bortezomib 1.3 mg/m² with dexamethasone 20 mg on the day of and day after bortezomib administration has produced a 100% OR rate, along with a CR/nCR rate of 52%.⁹ Various combination regimens involving the novel agents have now been elevated to NCCN Category 1, based on evidence from phase III clinical trials (Tables 4 and 5).

Table 4. Phase III Trials in Newly Diagnosed MM Among Patients Eligible for SCT: NCCN Level 1 Evidence

Study	N	Key Results	Key Points
Vincristine/dexamethasone (VD) vs vincristine/doxorubicin/dexamethasone (VAD) ⁴⁵	482	CR/nCR pre-ASCT: 21% vs 8% post-ASCT: 35% vs 24% VGPR pre-ASCT: 47% vs 19% post-ASCT: 62% vs 42%	VD was significantly more effective than VAD; VD equally effective for high-risk patients. VD is new standard for induction treatment. ⁹
Bortezomib/doxorubicin/dexamethasone (PAD) vs vincristine/doxorubicin/dexamethasone (VAD) ⁴⁶ <i>Interim analysis</i>	300	CR: 5% vs 0% ≥VGPR: 41% vs 17% ≥PR: 80% vs 64% After high-dose melphalan CR: 15% vs 4% ≥VGPR: 59% vs 47% ≥PR: 92% vs 77%	PAD yielded significantly more responses than did VAD (OR 27% vs 5%). Del 13 had no significant impact.
Bortezomib/thalidomide/dexamethasone (VTD) vs thalidomide/dexamethasone (TD) ⁴⁷	256	CR + nCR pre-ASCT: 36% vs 9% post-ASCT: 57% vs 28% ≥VGPR pre-ASCT: 60% vs 27% post-ASCT: 77% vs 54%	Adding bortezomib significantly improved RR across all categories.
Lenalidomide/dexamethasone (RD) vs dexamethasone (D) ⁴⁸	198	Results @ 1 y CR: 22% vs 4% OR: 84% vs 53% PFS: 77% vs 55%	RD superior to D; effective salvage with crossover also seen. Closed early because of evidence affecting acceptability of RD as control.

Table 5. Phase III Trials in Newly Diagnosed MM Among Patients Ineligible for SCT: NCCN Level 1 Evidence

Study	N	Key Results	Key Points
Bortezomib/melphalan/prednisone (VMP) vs melphalan/prednisone (MP) ^{21,49} <i>VISTA trial</i>	682	CR: 30% vs 4% PR: 71% vs 35% 3-year SR: 72% vs 59%	VMP superior to MP on all measures, including TTP, OR, CR, PFS, and time to next therapy.
Melphalan/prednisone/thalidomide (MPT) vs melphalan/prednisone (MP) ⁵⁰	331	CR: 16% vs 4% PR: 69% vs 48% PFS: 21.8 vs 14.5 mo	With median follow-up of 38.4 mo, MPT had better RR and remission duration <i>but</i> median OS for MPT was 45.0 mo vs 47.6 mo for MP; similarity in OS probably due to superior salvage regimens in MP group.
Lenalidomide/high-dose dexamethasone (RD) vs lenalidomide/low-dose dexamethasone (Rd) ³⁸	445	OR after 4 cycles: 79% vs 68% CR or VGPR: 42% vs 24% OS @ 24 mo: 75% vs 87%	RD produced superior response rates after first 4 cycles (≥PR 82% vs 70%) but greater toxicity (DVT: 26% vs 12%). Follow-up stopped at 12.5 mo because OS significantly greater with Rd than with RD.

CURRENT APPROACHES TO THERAPY IN MM: AN OVERVIEW

Regimens comprising thalidomide, bortezomib, and lenalidomide are now incorporated into the treatment of newly diagnosed, relapsed, and refractory myeloma. Moreover, these agents can be considered maintenance therapy for selected patients following induction with conventional therapy or induction followed by [ASCT](#) based on previously published clinical trials of thalidomide maintenance and ongoing clinical trials with lenalidomide and bortezomib in this setting.^{46,51} Choice of therapy is based on unique disease characteristics of the individual patient as well as preferences regarding mode of therapy and treatment administration. As discussed previously, the toxicity profiles of individual agents and agents in combination are also important determinants of therapy selection. Finally, the presence of specific comorbid conditions such as renal dysfunction, diabetes mellitus, cardiovascular disease, and disease-associated [PN](#) also influences treatment decisions to a significant extent.

Initial Therapy

As reflected by current [NCCN](#) recommendations, various thalidomide-, bortezomib-, and lenalidomide-containing regimens are appropriate for use as initial therapy for patients with newly diagnosed [MM](#). Two-drug regimens can be considered for transplant-ineligible patients with indolent disease, including those with few disease-associated symptoms and end-organ manifestations. On the other hand, three-drug regimens are more appropriate for those with high-risk features on the basis of International Staging System stage,

cytogenetic findings, and other factors associated with aggressive disease. Two-drug regimens also can be used for elderly or frail transplant-ineligible patients. Three-drug combinations are appropriate for elderly patients and others ineligible for **ASCT** who exhibit characteristics of high-risk disease. Bladé and Rosiñol have proposed a series of therapies for elderly patients according to patient and disease characteristics as typically applied in European practices (**Table 6**).⁵² Reasonable alternatives in US practice include **Rd** in less aggressive disease, with the addition of bortezomib as an appropriate option for more aggressive disease and consideration of weekly bortezomib to reduce **PN** also being important as part of any combination approach.

Efforts to reduce treatment-associated toxicity have been the focus of recent clinical investigations. As discussed above, **Rd** is preferred to **RD** because of superior **OS** that largely reflects a favorable side effect profile. Changes in the schedule of bortezomib are also being evaluated in ongoing studies. In a phase III trial of bortezomib/melphalan/prednisone versus that combination plus thalidomide, a weekly bortezomib schedule was associated with high levels of response and decreased toxicity (specifically **PN**).⁵³ Another phase III study compared bortezomib/melphalan/prednisone as induction therapy versus bortezomib/thalidomide/prednisone, followed by maintenance treatment with bortezomib/thalidomide versus bortezomib/prednisone. In this study, bortezomib was administered on a weekly schedule following an initial 6-week cycle in which the agent was administered according to the standard schedule. Both modified induction schedules were highly effective with similar **OR** and **CR** rates, but there was a clearly different toxicity profile among the regimens.⁵⁴ Specifically, bortezomib/melphalan/prednisone was associated with more neutropenia but less cardiac toxicity and **PN** than bortezomib/thalidomide/prednisone.⁵⁴

Table 6. Recommended Therapies for Elderly Patients in the European Union⁵²

Characteristic	Regimen
"Aggressive" disease	Melphalan/prednisone/bortezomib
"Less-aggressive" disease	Melphalan/prednisone/thalidomide
Adverse cytogenetics	Melphalan/prednisone/bortezomib
Renal failure	Bortezomib/dexamethasone
History of PN	Lenalidomide-based therapy
Age ≥75 years	Melphalan/prednisone/thalidomide (thalidomide 100 mg/d)

Adapted from Bladé J, Rosiñol L. *Haematologica*. 2009;94:163-166.

Treatment of Relapsed and Refractory MM

Because **MM** remains incurable, nearly all patients' disease relapses and becomes refractory to therapy. Determinants of therapy for patients with relapsed **MM** include prior treatment regimens, depth and duration of response to previous therapy, residual treatment-associated toxicity, the patient's age and overall physical condition, and specific features of disease progression, whether it be gradual or rapid. An agent that elicited a response in induction therapy can be reintroduced or used as part of a combination regimen for salvage, especially if the relapse occurred more than 6 months after the completion of prior therapy.⁸ For example, the 2008 update of the VISTA trial demonstrated that patients who received bortezomib induction subsequently responded to bortezomib-based therapy at time of relapse and were also highly responsive to immunomodulatory drug-based treatment.²¹

Patients who have had prior **ASCT** whose disease relapsed within 1 year or less after **ASCT** have a poor prognosis and should be encouraged to participate in clinical trials. Alternatively, these patients can be treated with intensive combination regimens that comprise at least one novel agent with 1 to 3 other drugs.^{55,56} Regimens tend to be most effective at first relapse rather than at later points in the disease.^{57,58} **Table 7** shows salvage therapies and their **NCCN** classifications.⁸

For carefully selected patients, a second **SCT** may be an option for salvage therapy; however, patients with adverse prognostic factors (including multiple lines of therapy and a **TTP** after initial transplant of ≤24 months) are unlikely to benefit significantly.⁵⁹ Generally, most experts recommend at least 2 to 3 years of **PFS** after the first **ASCT** for this approach to be justified.

Table 7. Salvage Therapies⁸

Regimen	NCCN Category
Bortezomib	1
Bortezomib/liposomal doxorubicin	1
Lenalidomide/dexamethasone	1
Bortezomib/dexamethasone	2A
Cyclophosphamide, vincristine, doxorubicin, dexamethasone	2A
Dexamethasone*	2A
Dexamethasone, cyclophosphamide, etoposide, cisplatin	2A
Thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide	2A
High-dose cyclophosphamide	2A
Lenalidomide	2A
Repeat primary induction therapy (if relapse at >6 mo)	2A
Thalidomide	2A
Thalidomide/dexamethasone	2A
Bendamustine-based therapy	2B
Lenalidomide/bortezomib/dexamethasone	2B

*High-dose dexamethasone as a single agent may have a limited role in stabilizing patients prior to additional therapy; in combination, lower doses can be used. As randomized clinical trials have consistently shown dexamethasone to be inferior to comparators such as bortezomib and lenalidomide/dexamethasone, its use cannot be recommended.

THE FUTURE

Over the past decade, the use of thalidomide, bortezomib, and lenalidomide has fundamentally changed the management of newly diagnosed as well as relapsed and refractory **MM**. These agents have significant single-agent activity, and combination regimens offer even higher levels of response without significant increases in treatment-associated toxicities. The development of these drugs has also stimulated interest in and development of new agents targeting pathways involved in the pathogenesis of **MM**. These include new immunomodulatory agents, more-selective proteasome inhibitors, histone deacetylase inhibitors, and other intracellular pathway inhibitors, as well as monoclonal antibodies. These developments promise to further improve the outcome for patients with **MM** in the years to come.

ABBREVIATIONS USED IN THIS PAPER (EXCLUDING DRUG NAMES)

ASCT: autologous stem cell transplant
 CR: complete response
 DVT: deep vein thrombosis
 MM: multiple myeloma
 NCCN: National Comprehensive Cancer Network
 nCR: near-complete response
 OR: overall response
 OS: overall survival
 PFS: progression-free survival
 PN: peripheral neuropathy
 PR: partial response
 SCT: stem cell transplant
 TTP: time to progression
 VGPR: very good partial response
 RD: lenalidomide/high-dose dexamethasone
 Rd: lenalidomide/low-dose dexamethasone

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